Message

**From**: EPA Pesticides Programs [oppt.epa@public.govdelivery.com]
**Sent**: 1/4/2017 7:17:31 PM
**To**: Anderson, Neil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8996b61c04ce4e5cb9e35b323ee5e824-Neil G. Anderson]
**Subject**: Pesticide Program Update: EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pet

# EPA Pesticide Program Updates

*From EPA's Office of Pesticide Programs*

*www.epa.gov/pesticides*

January 4, 2017

## In This Update:

### EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pets

EPA has finalized the human health risk assessment of tetrachlorvinphos (TCVP). TCVP is an organophosphate insecticide used to control fleas, ticks, and other pests on and around pets and livestock. It is used in residential products like pet collars.

Through the publication of the revised human health risk assessment and related documents, we are addressing a 2009 Natural Resource Defense Council (NRDC) petition.

This risk assessment identified potential risks to people, including children, in residential settings and to certain workers applying TCVP, which exceed the Agency's level of concern.

The Agency has contacted the pesticide manufacturers to initiate discussions with them to reduce exposure and resolve potential risks identified in the human health risk assessment. The Agency will issue a Proposed Decision in 2017 for public comment. Until that time, it is important to follow label instructions on proper use of pesticide products.

We advise consumers to take certain precautions when handling TCVP products in residential areas. These precautions are listed on TCVP product labels, including:

- not allowing children to play with TCVP pet collar products,
- keeping TCVP spray and powder products out of reach of children, and
- washing hands thoroughly with soap and water after handling.

To view TCVP's human health risk assessment and other registration review documents, visit regulations.gov, docket number EPA-HQ-OPP-2008-0316.

More information on:

- tetrachlorvinphos
- protecting your pets form fleas and ticks
- reducing your child's chances of pesticide poisoning

EPA distributes its Pesticide Program Updates to external stakeholders and citizens who have expressed an interest in the agency's pesticide program activities and decisions. This update service is part of EPA's continuing effort to improve public access to federal pesticide information.

For general questions about pesticides and pesticide poisoning prevention, contact the National Pesticide Information Center (NPIC), by email at npic@ace.orst.edu or, by visiting http://npic.orst.edu.

For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: http://www.epa.gov/pesticides.

You can unsubscribe or update your subscriptions or e-mail address at any time on your Subscriber Preferences Page. All you will need is your e-mail address. If you have any questions or problems, please e-mail subscriberhelp.govdelivery.com for assistance.

This service is provided to you at no charge by the U.S. Environmental Protection Agency.

This email was sent to anderson.neil@epa.gov using GovDelivery, on behalf of: U.S. EPA Office of Chemical Safety and Pollution Prevention · 408 St. Peter Street, Suite 600 · Saint Paul, MN 55102 · 1-800-439-1420

Message

**From**: Charlotte Sanson [charlotte.sanson@bayer.com]
**Sent**: 9/22/2016 1:49:17 PM
**To**: Anderson, Neil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8996b61c04ce4e5cb9e35b323ee5e824-Neil G. Anderson]
**CC**: Guilaran, Yu-Ting [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a698774e93e34a2b9181d4b3032b8a32-ytguilar]; Karen Shearer [karen.shearer@bayer.com]; Doug Spilker [doug.spilker@bayer.com]
**Subject**: Mintues from PRD and Bayer Meeting of Aug. 31st
**Attachments**: 2016-8-31_PRD-OPP_BCS_Meeting_with_EPA_minutes.docx

Hello Neil.

Many thanks to the PRD team for meeting with Bayer on August 31st to review the status of compounds in Registration Review. The attached document reflects our understanding of the discussion. If you would please forward to the attendees, and respond with needed edits directly in this file. We will then submit a finalized version.

Thanks again.

Best regards,

Charlotte Sanson
Director Registrations

Science For A Better Life

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**Bayer CropScience – OPP/PRD Meeting Agenda**
**August 31, 2016**

**Status Updates for Compounds in Registration Review**

EPA Attendees:

| | |
|---|---|
| Ricardo Jones | Veronica Dutch |
| Kelly Ballard | Melissa Grable |
| James Parker | Brian Kettl |
| Kelly Sherman | Lindsey Walsh |
| Tracy Perry | Margaret Hathaway |
| Yu-Tin Guilaran | Bilin Basu |
| Linda Arrington | Bo Davis |
| Jill Bloom | Neil Anderson |
| Maria Piansay | |

Bayer Attendees:

| | |
|---|---|
| Karen Shearer | |
| Doug Spilker | |
| Charlotte Sanson | |
| On phone from Bayer: | |
| Karen Cain | Lisa Bowers |
| Nancy Delaney | Sean McGee |
| Jessica Fernandez | Annette Bloomberg |
| Amy McCaskill | Alex Nikolakis |
| Danyel Ward | Jan Brill |

## Herbicides

1. **Glufosinate** (PC Code 128850): The proposed interim decision was issued middle of July 2016 with comments due middle of September 2016.
   - Does PRD have an estimate on how much time will be needed to review and respond to the comments?
     *EPA Response*: Comments are in review, aiming to issue Response To Comments in conjunction with final interim decision by December.
   - What is PRD's target for issuing the final interim decision?
     *EPA Response*: Planned for December 2016.
   - Bayer is voluntarily cancelling registration of the rice uses. What is the process for maintaining the rice tolerances for import purposes?
     *EPA Response*: EPA will issue a FIFRA 6(f) notice of receipt of the cancellation. EPA will initiate the process for changing the rice tolerance to an import tolerance. Since this is an Agency initiated action, there is no PRIA fee due from Bayer.
   - Additionally, we have recently filed a 6a2 report from a recent magnitude of residue study on pistachios indicating the tolerances on pistachio should be increased. Should these actions be combined (retaining rice tolerance for import and increasing pistachio tolerance based on new data)?
     *EPA Response*: These actions will be handled separately. The pistachio tolerance increase will be handled as a PRIA action, being initiated by Bayer.

2. **Isoxaflutole** (PC Code 123000): Completion of the RD action for HT-tolerant soybeans is pending refined ecological risk assessment incorporating new nozzle data (ultra coarse nozzles) and review of the benefits document.
   *EPA Response*: As the CRM was not available for the meeting, PRD will follow up separately to answer.
   - How does PRD coordinate with RD on this?
   - What is the status/time line?

3. **HPPD's:** What is EPA's timeline to review the supplemental data that registrants have provided?
   *EPA Response*: The data is in review, timeline not yet known. PRD will discuss with HED.

4. **SU's**: On August 19, 2016, the Ad Hoc Work Group submitted a request to extend the public comment period for the Preliminary Interim Decision (PID) from ending on September 12, 2016 to January 10, 2017. Several reasons were cited including 1) that the PIDs were published in the middle of the growing season, making it difficult to consult with key stakeholders; 2) more time is required to review over 425 end use product labels to assess the impact to efficacy and crop safety with respect to the PID prescribed label changes; 3) to allow time for the Work Group to meet with the Agency to discuss options for label mitigation other than extremely coarse droplet size; and 4) to allow time for the public comment period on the Resistance Management PR Notice to close and for the EPA to consider comments before implementing final guidance.
   - What is the status of the time extension request?
     *EPA Response*: PRD received the time extension request August 22nd and responded to Jake Vukich (DuPont, serving as the industry lead) on August 25th. PRD felt that a fair assessment had been done and asked for an explanation for the basis of the requested 4 month extension. Bayer explained that there may be concerns with regard to efficacy related to spray nozzles that have not yet been tested. EPA commented that discussion on label amendments can continue after the due date for the response. (Since the meeting, Bayer learned that EPA has granted a time extension of 45 days for submission of responses.)

5. **Phenmedipham** (PC Code 098701): On July 14, 2016, Bayer submitted the 90-day response to the Generic Data Call-In, including a low volume waiver request.
   - As this is our first experience in submitting this type of waiver, is feedback available on the content and rationale? Is a status update available?
     *EPA Response*: PRD is reviewing the rationale with EFED and BEAD. Existing studies were cited which are also being considered. The information appears adequate to make a determination. PRD will issue a response in about a month.

## Fungicides

No questions at this time.

## Insecticides

1. **Imidacloprid** (PC Code 129099): It appears that not all imidacloprid technical registrants are members of the imidacloprid DCI cost-sharing consortium.
   - How does EPA plan to address the DCI requirements to be fulfilled by those registrants not in the consortium?
     *EPA Response*: Inform PRD if we are aware of registrants who have committed to to cost share but are not participating in the consortium.
   - Is our understanding of the following critical milestones correct?
     - Updated pollinator risk assessment and comprehensive risk assessments (HED and EFED) to be released for public comment by the end of 2016.
       *EPA Response*: Yes, on track.
     - Proposed registration decision to be issued for public comment by mid-2017.
       *EPA Response:* A 3rd pollinator assessment will be done to evaluate incoming data from higher tier studies. Thus, the public comment period will likely occur in 2018.
     - Final registration decision to be released for public comment by mid-2018.
       *EPA Response*: Will extend into 2019.
   - What are EPA's current plans and scheduling for label mitigation?
     - Would EPA request label mitigation for imidacloprid alone or do so simultaneously with other neonics?
       *EPA Response:* This class of chemistry will be reviewed together (see below).
     - How will EPA require all imidacloprid registrants to comply with label mitigation at the same time?
       *EPA Response:* Some neonic products are alternatives to others. EPA will take into consideration uses where this is not the case with regard to label mitigation.
   - Bayer has concerns related to the current modeling being used to assess imidacloprid in EFED's aquatic invertebrate risk assessment. We have requested a meeting to address, and would like to work with PRD to schedule. Further background information will be provided to PRD during the meeting on August 31st.
     *EPA Response:* Bayer to follow up with proposed dates in September. (A meeting has since been scheduled, for October 13th).

2. **Pyrethroid's** (Bifenthrin, Cyfluthrins , Deltamethrin, Esfenvalerate, Fenpropathrin, Cyhalothrins, Permethrin, Cypermethrins, and Tefluthrin): Bayer requests clarification regarding the process and timeline of publication of the pyrethroid Environmental Toxicology Assessment and individual compound Health Effects Assessments for public comment.
   - Will all pyrethroid active ingredient risk assessments be posted at the same time or for a few/several a.i.s at a time?
     *EPA Response:* At different times. What will be the sequence if not at the same time?
     *EPA Response:* EFED for PWG actives published in September 2016; HED for non-PWG actives in September 2016; HED for PWG actives in December 2016; PID for pyrethroids in March 2017.
   - If the two assessments (i.e., Environment and Health Effects) are posted at separate times, will there also be two separate comment periods? *EPA Response:* Yes. For the same length/duration? *EPA Response:* 60 days.
   - With regard to posting comments to the docket, will stakeholders be permitted to post in a similar format as the SU's, i.e., stakeholders posted comments to one docket but comments can cover all compounds which were identified by Docket number. Did this process work for the Agency for the SU's? *EPA Response*: Yes to both questions.

3. **Spirodiclofen** (PC Code 124871): On August 18th, Bayer submitted a low volume waiver with our proposed phase out plan for this compound.
   - Can the Agency provide feedback regarding the process for this review and when we might expect an answer?
     *EPA Response:* The information submitted appears adequate, and PRD will likely issue a response in 3-4 weeks.

4. **Carbaryl** (PC Code – 057901): Please confirm that EPA is on track to release the ecological risk assessment by end of 2016.
   *EPA Response:* Yes.

5. **Trichlorofon** (PC Code – 056801): Please confirm that EPA is on track to release the ecological risk assessment by end of 2016.
   *EPA Response*: Yes.

6. **Coumaphos** (PC Code 036501): The Preliminary Interim Decision is still expected in December 2016. Bayer requests assurance that the documents we provided in July to the docket or directly in response to Risk Assessments have been routed within the Agency for consideration in developing the Interim Decision Document.
   *EPA Response:* The Preliminary Interim Decision is still expected in December 2016. The five documents provided in July to the docket or directly in response to Risk Assessments have been routed within the Agency for consideration in developing the PID. Mr. Kettl will check to ensure all were entered into the docket, except the one which CBI.

7. **Tetrachlorvinphos** (PC Code 083702): Bayer requests assurance that the documents we provided in March/April to the docket or directly in response to Risk Assessments have been routed within the Agency for consideration in developing the Interim Decision Document.
   *EPA Response:* The Preliminary Interim Decision is still expected in December 2016. The two documents provided in March/April to the docket or directly in response to risk assessments have been routed within the Agency for consideration in developing the PID.

8. **Flumethrin** (PC Code 128968): The "Registration Review Schedules" website indicates the Draft Risk Assessment for Flumethrin is to be issued FY16 Quarter 4, even though the active ingredient was just registered for the first time in 2012. We have not been notified that this was happening, and no docket has yet been opened. Bayer requests clarification on why this is being done outside of the usual Registration Review process, i.e. why not a docket opening/DCI before directly to Draft Risk Assessments?
   *EPA Response:* The Preliminary WorkPlan will open with the typical Registration Review process. The docket is expected to open by the end of September, includling a scoping document addressing health concerns, along with the ecological risk assessment which has already been done.

## Other Topics

1. Process Comments/Questions:
   - How is coordination on compounds managed between PRD and RD?
     *EPA Response:* Progress has been made, and the two divisions continue actively working on this.
   - Preliminary work plans are often released with no advance notice to registrants. We are concerned that we could miss or have limited time to respond during the comment period. Examples include Oxadiazon, Triadimefon and Triadimenol, and Ethofumesate. Can PRD please notify registrants when PWP's are issued?
     *EPA Response:* PRD intends to inform registrants. Registrants can also set up a notification in regulations.gov website to be notified when a posting occurs to the docket.
   - We have experienced a case (propoxycarbazone-sodium) where the Preliminary Work Plan was issued without including the problem formulation, and the Interim Decision was published before the DCI was issued. Can PRD provide an explanation? Would this type of information be shared in a focus meeting?
     *EPA Response:* In this case, the PWP and human health risk assessment were combined since no additional human health effects data was needed. Pollinator data only is relevant to the DCI.

2. Bayer is concerned about the resources required to manage the label amendments within 60 days following publication of the final interim decisions since several are expected at the same time (mesosulfuron-methyl, iodosulfuron-methyl, foramsulfuron, flufenacet, propoxycarbazone-sodium).
   - Is the EPA open to a submission schedule based on certain criteria, for example, marketed products versus non-marketed products?
     *EPA Response:* The registrant can inform EPA, however EPA does not treat non-commercialized product labels differently from those that are marketed.
   - How will all registrants be notified of required changes to the labels?
     *EPA Response:* Registrants will get a letter with the same 60-day response requirement; EPA may entertain a time extension if requested.
   - Are technical registrants responsible to contact other end use product registrants?
     *EPA Response:* EPA will inform all registrants who have registered products that are impacted.
   - Will the approval letter state 12 months, or 18 months, to make the required changes on the commercial label? Will there be the "at next printing" requirement in the approval letter?
     *EPA Response:* The standard 18-month rule applies for products released for shipment. PRD and RD have worked out a process to review labels; PRD typically provides labels to RD in batches. The released for shipment language the Agency has provided in previous label approvals is "After 18 months, you may only distribute or sell this product if it bears this new revised labeling or subsequently approved labeling." "To distribute or sell" is defined under FIFRA section 2(gg) and its implementing regulation at 40 CFR 152.3.

3. DCI responses currently require registrants to commit (response "1") to completing higher tiered studies in unrealistic timeframes and prior to completion of the tier 1 studies that may or may not trigger them. EPA's timeline for pollinator studies is not achievable unless all Tier 1, 2 and 3 work is initiated in parallel in the 1st year. This "start everything at once" approach is not scientifically valid or in line with EPA's own guidance. Bayer intends to complete the Tier 1 lab studies on the required timeline (12 months), evaluate the results, confer with the Agency, and then do more work, if triggered by the risk assessment. Therefore we have been routinely submitting waivers (response "9") for Tier 2 and 3 pollinator data requirements. Does the Agency agree with this approach?
   *EPA Response:* A stepwise process for addressing triggered data requirements is addressed in the footnotes of a DCI. Requesting a waiver initially is the appropriate approach. There is an understanding that time extensions are practical in those cases where a data requirement is triggered and the due date needs to be adjusted; in such a case, the registrant should request a time extension.

Appointment

**From**: Microsoft Outlook [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=MICROSOFTEXCHANGE329E71EC88AE4615BBC36AB6CE41109EF7088051]
**Sent**: 1/18/2017 5:21:15 PM
**To**: Anderson, Neil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8996b61c04ce4e5cb9e35b323ee5e824-Neil G. Anderson]

**Subject**: Meeting Forward Notification: Discuss TCVP Petition Response Plan
**Location**: DCRoomPYS9100/Potomac-Yard-One

**Start**: 1/25/2017 3:00:00 PM
**End**: 1/25/2017 4:00:00 PM

**Recurrence**: (none)

## Your meeting was forwarded

Drew, Danette has forwarded your meeting request to additional recipients.

Meeting

Discuss TCVP Petition Response Plan

Meeting Time

Wednesday, January 25, 2017 10:00 AM-11:00 AM.

Recipients

Britton, Wade

All times listed are in the following time zone: (UTC-05:00) Eastern Time (US & Canada)

Sent by Microsoft Exchange Server

Message

**From**: Charlotte Sanson [charlotte.sanson@bayer.com]
**Sent**: 8/31/2016 2:02:05 PM
**To**: Anderson, Neil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8996b61c04ce4e5cb9e35b323ee5e824-Neil G. Anderson]
**CC**: Karen Shearer [karen.shearer@bayer.com]; Doug Spilker [doug.spilker@bayer.com]
**Subject**: Slides for Today's Meeting
**Attachments**: EPA PRD meeeting Aug 31 2016.pptx

Hi Neil,

The attached slides give a high level overview of the status of Bayer's compounds in Reg Review. We'll show this at the beginning of the meeting but won't discuss in detail due to time constraints.

Will contact you from the lobby @1:15.

Thanks.

Best regards,

Charlotte Sanson
Director Registrations

Science For A Better Life

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BCS-REG-REGU, Registrations
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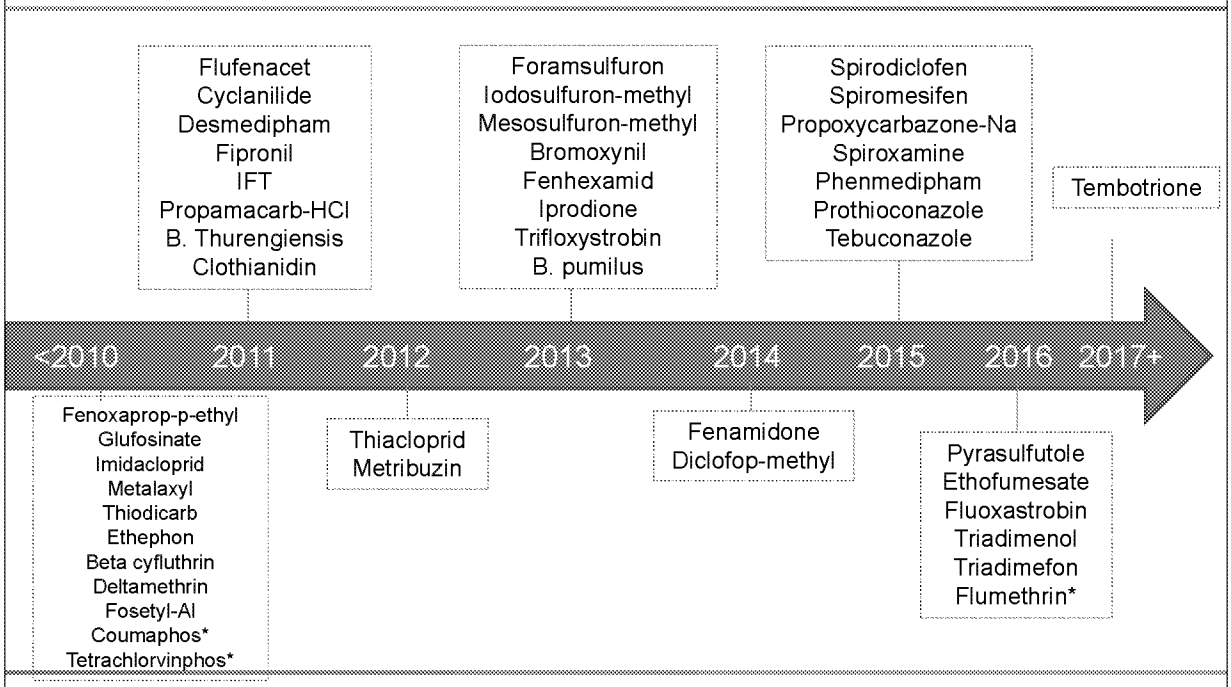
# Registration Review for BCS Chemicals (year initiated)




August 31, 2016

*Bayer Animal Health

# US Registration Review Status

| Milestone | A.I.'s Impacted | Remaining Action(s) |
|---|---|---|
| **Data Call-In (issued, to be issued, or response required Q3/Q4 2016)** | Ethofumesate, Phenmedipham*, Spiromesifen, Spirodiclofen*, Tebuconazole, Prothioconazole | • Resource planning, DCI response<br>• *BCS requested low volume waivers |
| **Risk Assessments** | Beta cyfluthrin, Deltamethrin, Bromacil, Flumethrin(?) | |
| **Proposed Interim Decisions issued (July 14, 2016)** | Bromoxynil, Chlorsulfuron, Flufenacet, Foramsulfuron, Glufosinate ammonium, Iodosulfuoron methyl, Mesosulfuron methyl, Nicosulfuron, Rimsulfuron, Sulfometuron methyl, | • Responses due to EPA Sept. 12, 2016<br>• 42 end-use product labels potentially impacted upon issuance of final interim decision Q1 2017 (resist. management, drift/run-off advisory) |

# US Registration Review Status

| Milestone | A.I.'s Impacted | Remaining Action(s) |
|---|---|---|
| **Final Interim Decisions expected before end of 2016** | Propoxycarbazone-sodium | • Prepare and submit amended labels based on required mitigation<br>• Action required for 7 end-use product labels (264-809, -808, -833, -847, -1099, 432-1584) |
| **Proposed Interim Decisions Expected 2016[1], 2017[2], 2018[3]** | Imidacloprid[2], Clothianidin[3], Propamacarb HCl[2], Fenamidone[3], Cyfluthrins[2], Ethephon[1], Cyclanilide[1], Thidiazuron[1], Coumaphos[1], Tetrachlorvinphos[1] | • Asset team review, response prep |
| **Final Interim Decisions Issued to Date** | Fenoxaprop-p-ethyl<br>Fosetyl-Al | • EPA conducting endangered species assessment |

August 31, 2016

Message

**From**: Charlotte Sanson [charlotte.sanson@bayer.com]
**Sent**: 8/25/2016 6:23:02 PM
**To**: Anderson, Neil [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8996b61c04ce4e5cb9e35b323ee5e824-Neil G. Anderson]
**CC**: Karen Shearer [karen.shearer@bayer.com]; Doug Spilker [doug.spilker@bayer.com]
**Subject**: RE: Request for Brief Discussion
**Attachments**: 2016-8-31_PRD-OPP_BCS_Meeting_with_EPA_Agenda.pdf

Thanks, Neil. Much appreciated.

The topics to be discussed are listed in the attached document. Some process questions may still come up so I'll add and forward before Wednesday if that's the case. We will also show a couple slides that illustrate a high level overview of the status of all Bayer compounds in Reg Review. Still working on it, and will forward to you in advance of the meeting.

Karen Shearer and Doug Spilker will join me in person, and other team members will join by phone. Should we give you a call upon arrival in the lobby on Wednesday?

Best regards,

Charlotte Sanson
Director Registrations

Science For A Better Life

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BCS-REG-REGU, Registrations
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E-mail: charlotte.sanson@bayer.com
Web: http://www.bayer.com

**From:** Anderson, Neil [mailto:Anderson.Neil@epa.gov]
**Sent:** Thursday, August 25, 2016 8:25 AM
**To:** Charlotte Sanson
**Subject:** RE: Request for Brief Discussion

I will set up the conference line. So you know what it is and can share ahead of time here it is:

**Personal Matters / Ex. 6**

*The information contained in this e-mail is for the exclusive use of the intended recipient(s) and may be confidential, proprietary, and/or legally privileged. Inadvertent disclosure of this message does not constitute a waiver of any privilege. If you receive this message in error, please do not directly or indirectly use, print, copy, forward, or disclose any part of this message. Please also delete this e-mail and all copies and notify the sender. Thank you.*

# Bayer CropScience – OPP/PRD Meeting Agenda
# August 31, 2016

## Status Updates for Compounds in Registration Review

### Herbicides

1. **Glufosinate** (PC Code 128850): The proposed interim decision was issued middle of July 2016 with comments due middle of September 2016.
   - Does PRD have an estimate on how much time will be needed to review and respond to the comments?
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   - As this is our first experience in submitting this type of waiver, is feedback available on the content and rationale? Is a status update available?

### Fungicides

No questions at this time.

## Insecticides

1. **Imidacloprid** (PC Code 129099): It appears that not all imidacloprid technical registrants are members of the imidacloprid DCI cost-sharing consortium.
   - How does EPA plan to address the DCI requirements to be fulfilled by those registrants not in the consortium?
   - Is our understanding of the following critical milestones correct?
     - Updated pollinator risk assessment and comprehensive risk assessments (HED and EFED) to be released for public comment by the end of 2016.
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     - Final registration decision to be released for public comment by mid-2018.
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     - Would EPA request label mitigation for imidacloprid alone or do so simultaneously with other neonics?
     - How will EPA require all imidacloprid registrants to comply with label mitigation at the same time?
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   - Will all pyrethroid active ingredient risk assessments be posted at the same time or for a few/several a.i.s at a time? What will be the sequence if not at the same time?
   - If the two assessments (i.e., Environment and Health Effects) are posted at separate times, will there also be two separate comment periods? For the same length/duration?
   - With regard to posting comments to the docket, will stakeholders be permitted to post in a similar format as the SU's, i.e., stakeholders posted comments to one docket but comments can cover all compounds which were identified by Docket number. Did this process work for the Agency for the SU's?

3. **Spirodiclofen** (PC Code 124871): On August 18th, Bayer submitted a low volume waiver with our proposed phase out plan for this compound.
   - Can the Agency provide feedback regarding the process for this review and when we might expect an answer?

4. **Carbaryl** (PC Code – 057901): Please confirm that EPA is on track to release the ecological risk assessment by end of 2016.

5. **Trichlorofon** (PC Code – 056801): Please confirm that EPA is on track to release the ecological risk assessment by end of 2016.

6. **Coumaphos** (PC Code 036501): The Interim Decision is expected in December 2016. Bayer requests assurance that the documents we provided in July to the docket or directly in response to Risk Assessments have been routed within the Agency for consideration in developing the Interim Decision Document.

7. **Tetrachlorvinphos** (PC Code 083702): Bayer requests assurance that the documents we provided in March/April to the docket or directly in response to Risk Assessments have been routed within the Agency for consideration in developing the Interim Decision Document.

8. **Flumethrin** (PC Code 128968): The "Registration Review Schedules" website indicates the Draft Risk Assessment for Flumethrin is to be issued FY16 Quarter 4, even though the active ingredient was just registered for the first time in 2012. We have not been notified that this was happening, and no docket has yet been opened. Bayer requests clarification on why this is being done outside of the usual Registration Review process, i.e. why not a docket opening/DCI before directly to Draft Risk Assessments?

## Other Topics

1. Process Comments/Questions:
   - How is coordination on compounds managed between PRD and RD?
   - Preliminary work plans are often released with no advance notice to registrants. We are concerned that we could miss or have limited time to respond during the comment period. Examples include Oxadiazon, Tridimenfon and Triadimenol, and Ethofumesate. Can PRD please notify registrants when PWP's are issued?
   - We have experienced a case (propoxycarbazone-sodium) where the Preliminary Work Plan was issued without including the problem formulation, and the Interim Decision was published before the DCI was issued. Can PRD provide an explanation? Would this type of information be shared in a focus meeting?

2. Bayer is concerned about the resources required to manage the label amendments within 60 days following publication of the final interim decisions since several are expected at the same time (mesosulfuron-methyl, iodosulfuron-methyl, foramsulfuron, flufenacet, propoxycarbazone-sodium).
   - Is the EPA open to a submission schedule based on certain criteria, for example, marketed products versus non-marketed products?
   - How will all registrants be notified of required changes to the labels?
   - Are technical registrants responsible to contact other end use product registrants?
   - Will the approval letter state 12 months, or 18 months, to make the required changes on the commercial label? Will there be the "at next printing" requirement in the approval letter?

3. DCI responses currently require registrants to commit (response 1) to completing higher tiered studies in unrealistic timeframes and prior to completion of the tier 1 studies that may or may not trigger them. EPA's timeline for pollinator studies is not achievable unless all Tier 1, 2 and 3 work is initiated in parallel in the 1st year. This "start everything at once" approach is not scientifically valid or in line with EPA's own guidance. Bayer intends to complete the Tier 1 lab studies on the required timeline (12 months), evaluate the results, confer with the Agency, and then do more work, if triggered by the risk assessment. Therefore we have been routinely submitting waivers (response 9) for Tier 2 and 3 pollinator data requirements. Does the Agency agree with this approach?

Message

**From**: RAB57 - HED/OPP [no-reply@sharepointonline.com]
**Sent**: 10/11/2016 6:30:57 PM
**To**: Drew, Danette [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2a99dc94fd974fb6a26f9e35829f881c-Danette Drew]
**Subject**: RAB57 Peer Review - TCVP revised dietary Final Draft has been assigned to you

RAB57 - HED/OPP

# ***TCVP revised dietary Final Draft*** has been assigned to you

Modify my alert settings | View TCVP revised dietary Final Draft | View RAB57 Peer Review | Mobile View

| | |
|---|---|
| **Title:** | TCVP revised dietary Final Draft |
| **Predecessors:** | |
| **Priority:** | (2) Normal |
| **Task Status:** | Not Started |
| **% Complete:** | 0% |
| **Document Created By:** | Drew, Danette |
| **Assigned To:** | Drew, Danette |
| **Description:** | TCVP revised dietary Final Draft version |
| **Start Date:** | 10/11/2016 |
| **Due Date:** | 10/12/2016 |
| **Completed:** | No |
| **Peer Review Type:** | Dietary Memos for Branch QA-QC |

Last Modified 10/11/2016 2:30 PM by Drew, Danette

Message

**From**: EPA Pesticides Programs [oppt.epa@public.govdelivery.com]
**Sent**: 1/4/2017 7:17:31 PM
**To**: Grable, Melissa [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=017278065a7c4cd68f85ecaff5596788-Grable, Melissa]
**Subject**: Pesticide Program Update: EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pet

# EPA Pesticide Program Updates

*From EPA's Office of Pesticide Programs*

*www.epa.gov/pesticides*

January 4, 2017

## In This Update:

### EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pets

EPA has finalized the human health risk assessment of tetrachlorvinphos (TCVP). TCVP is an organophosphate insecticide used to control fleas, ticks, and other pests on and around pets and livestock. It is used in residential products like pet collars.

Through the publication of the revised human health risk assessment and related documents, we are addressing a 2009 Natural Resource Defense Council (NRDC) petition.

This risk assessment identified potential risks to people, including children, in residential settings and to certain workers applying TCVP, which exceed the Agency's level of concern.

The Agency has contacted the pesticide manufacturers to initiate discussions with them to reduce exposure and resolve potential risks identified in the human health risk assessment. The Agency will issue a Proposed Decision in 2017 for public comment. Until that time, it is important to follow label instructions on proper use of pesticide products.

We advise consumers to take certain precautions when handling TCVP products in residential areas. These precautions are listed on TCVP product labels, including:

- not allowing children to play with TCVP pet collar products,
- keeping TCVP spray and powder products out of reach of children, and
- washing hands thoroughly with soap and water after handling.

To view TCVP's human health risk assessment and other registration review documents, visit regulations.gov, docket number EPA-HQ-OPP-2008-0316.

More information on:

- tetrachlorvinphos
- protecting your pets form fleas and ticks
- reducing your child's chances of pesticide poisoning

EPA distributes its Pesticide Program Updates to external stakeholders and citizens who have expressed an interest in the agency's pesticide program activities and decisions. This update service is part of EPA's continuing effort to improve public access to federal pesticide information.

For general questions about pesticides and pesticide poisoning prevention, contact the National Pesticide Information Center (NPIC), by email at npic@ace.orst.edu or, by visiting http://npic.orst.edu.

For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: http://www.epa.gov/pesticides.

You can unsubscribe or update your subscriptions or e-mail address at any time on your Subscriber Preferences Page. All you will need is your e-mail address. If you have any questions or problems, please e-mail subscriberhelp.govdelivery.com for assistance.

This service is provided to you at no charge by the U.S. Environmental Protection Agency.

This email was sent to grable.melissa@epa.gov using GovDelivery, on behalf of: U.S. EPA Office of Chemical Safety and Pollution Prevention · 408 St. Peter Street, Suite 600 · Saint Paul, MN 55102 · 1-800-439-1420

Message

**From**: Sherry Hull [shull@bacwa.org]
**Sent**: 1/2/2017 6:24:26 AM
**To**: Housenger, Jack [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e5840e7ccea94f6b89471abd355dceb7-Jack E. Housenger]
**Subject**: FW: Flumethrin Preliminary Work Plan, Case # 7456 (Docket ID Number EPA–HQ–OPP–2016–0031)
**Attachments**: BACWA Flumethrin Ltr 20DEC2016 with Attachmts due 1-3-17.pdf

Dear Jack,

Please see below. I sent this email to an incorrect email address for you previously.

Best regards,
Sherry

---

**From:** Sherry Hull
**Sent:** Sunday, January 1, 2017 9:13 PM
**To:** 'Piansay.maria@Epa.gov' <Piansay.maria@Epa.gov>
**Cc:** 'Guilaran.yu-Ting@Epa.gov' <Guilaran.yu-Ting@Epa.gov>; 'ousenger.jack@epa.gov' <ousenger.jack@epa.gov>; 'perry.tracy@epa.gov' <perry.tracy@epa.gov>; 'keigwin.richard@epa.gov' <keigwin.richard@epa.gov>; 'costello.kevin@epa.gov' <costello.kevin@epa.gov>; 'Arrington.linda@Epa.gov' <Arrington.linda@Epa.gov>; 'Biscoe.melanie@Epa.gov' <Biscoe.melanie@Epa.gov>; 'Shamim.mah@Epa.gov' <Shamim.mah@Epa.gov>; 'Steeger.thomas@Epa.gov' <Steeger.thomas@Epa.gov>; 'Holmes.jean@Epa.gov' <Holmes.jean@Epa.gov>; 'Waleko.Garland@epa.gov' <Waleko.Garland@epa.gov>; 'sawyers.andrew@epa.gov' <sawyers.andrew@epa.gov>; 'torres.tomas@epa.gov' <torres.tomas@epa.gov>; 'denton.debra@epa.gov' <denton.debra@epa.gov>; 'tenbrook.patti@epa.gov' <tenbrook.patti@epa.gov>; 'Dawit.Tadesse@waterboards.ca.gov' <Dawit.Tadesse@waterboards.ca.gov>; 'Noelle.Patterson@waterboards.ca.gov' <Noelle.Patterson@waterboards.ca.gov>; 'tmumley@waterboards.ca.gov' <tmumley@waterboards.ca.gov>; 'JOHara@waterboards.ca.gov' <JOHara@waterboards.ca.gov>; 'James.Parrish@waterboards.ca.gov' <James.Parrish@waterboards.ca.gov>; 'George.Farnsworth@cdpr.ca.gov' <George.Farnsworth@cdpr.ca.gov>; 'Nan.Singhasemanon@cdpr.ca.gov' <Nan.Singhasemanon@cdpr.ca.gov>; 'Jennifer.Teerlink@cdpr.ca.gov' <Jennifer.Teerlink@cdpr.ca.gov>; 'kmoran@tdcenvironmental.com' <kmoran@tdcenvironmental.com>; 'chornback@nacwa.org' <chornback@nacwa.org>; 'CFinley@NACWA.ORG' <CFinley@NACWA.ORG>; 'Amy J. Chastain (AChastain@sfwater.org)' <AChastain@sfwater.org>; 'Ben Horenstein' <bhorenst@ebmud.com>; 'Dave Stoops (Dastoops@ebda.org)' <Dastoops@ebda.org>; 'Ervin, James' <James.Ervin@sanjoseca.gov>; 'Jason Warner (jwarner@oroloma.org)' <jwarner@oroloma.org>; 'Jean-Marc Petit' <jmpetit@centralsan.org>; 'Laura Pagano (LPagano@sfwater.org)' <LPagano@sfwater.org>; 'Lori Regler (lregler@sfwater.org)' <lregler@sfwater.org>; 'Lori Schectel' <lschectel@centralsan.org>; 'Maura Bonnarens (mbonnare@ebmud.com)' <mbonnare@ebmud.com>; 'Mike Connor (mconnor@ebda.org)' <mconnor@ebda.org>; Mutsuddy, Amit <amit.mutsuddy@sanjoseca.gov>; 'Roger Bailey' <rbailey@centralsan.org>; 'Tommy Moala' <tmoala@sfwater.org>; 'Vincent De Lange (vdelange@ebmud.com)' <vdelange@ebmud.com>
**Subject:** Flumethrin Preliminary Work Plan, Case # 7456 (Docket ID Number EPA–HQ–OPP–2016–0031)

Dear Ms. Piansay,

On behalf of David R. Williams, P.E. and Executive Director of the Bay Area Clean Water Agencies (BACWA), please find attached a Comment Letter on the preliminary work plan for flumethrin, a pet flea control pesticide that was submitted today via the EPA website (Comment Tracking Number: 1k1-8txh-hte7).

Let me know if you have any questions or concerns.

Best regards & Happy New Year,
Sherry

*Sherry Hull*
*Assistant Executive Director*
**Bay Area Clean Water Agencies**
shull@bacwa.org
415-404-8303

BACWA
BAY AREA
CLEAN WATER
AGENCIES

DUE DATE: January 3, 2017

Maria Piansay, *piansay.maria@epa.gov*
Risk Management and Implementation
Pesticide Re-evaluation Division (7508P)
Office of Pesticide Programs (OPP)
U.S. Environmental Protection Agency (U.S. EPA)
1200 Pennsylvania Ave., NW.
Washington, DC 20460–0001

**Subject: Flumethrin Preliminary Work Plan, Case # 7456 (Docket ID Number EPA–HQ–OPP–2016–0031)**

Dear Ms. Piansay:

On behalf of the Bay Area Clean Water Agencies (BACWA), we thank you for the opportunity to comment on the preliminary work plan for flumethrin, a pet flea control pesticide.

BACWA's members include 55 publicly owned wastewater treatment facilities ("POTWs") and collection system agencies serving 7.1 million San Francisco Bay Area residents. We take our responsibilities for safeguarding receiving waters seriously. BACWA is especially interested in pesticides, like pet flea control products, that are used in manners that have transport pathways to the sanitary sewer, as even the most sophisticated wastewater treatment plants cannot fully remove complex chemicals like pesticides.

OPP has historically omitted evaluation of risks associated with pesticide discharges to the sewer system. Omitting evaluation of the sewer discharge environmental exposure pathway can prove costly for POTWs, due to the potential for pesticides to cause or contribute to wastewater treatment process interference, NPDES Permit compliance issues, impacts to receiving waters, recycled water quality and/or biosolids reuse, in addition to exposing POTWs to the potential for third party lawsuits under the Clean Water Act.

Flumethrin appears to be among many "topical" (collars and spot-on) pesticides for companion animals that U.S. EPA is considering in its Registration Review process. The primary purpose of this letter is to request an ecological risk assessment to evaluate sewer discharges from pet collars and call for the aquatic toxicity and environmental exposure and fate data necessary for a quantitative assessment. We also summarize information about the transport of topical pet applications to the sanitary sewer and provide our recommendations for POTW "down-the-drain" modeling for pet collar and spot-on discharges.

**BACWA's Interest in Flumethrin and Other Pet Treatments**

Flumethrin, a synthetic pyrethroid, is the active ingredient in a pet collar for flea, tick, and lice control on cats and dogs (at a concentration of 4.5% and combined with a second active ingredient, 10% imidacloprid). Topical (collar and spot-on) treatments are a common method of flea control.[1] According to the U.S. Census Bureau, there are 0.27 cats per capita in the US.[2] Industry market data indicate that 75 percent of pet owners use a pet flea control treatment.[3] BACWA member agencies recently participated in a scientific study conducted by the San Francisco Bay Regional Monitoring Program that identified two pet flea control pesticides with otherwise limited indoor use (fipronil and imidacloprid) in wastewater influent, effluent, and biosolids, and suggested that topical pet products may be their primary source.[4]

**Transport of Pet Treatment Residues to Sanitary Sewer**

There is evidence that topical pet treatments result in discharges to the sanitary sewer. Regarding flumethrin in pet collar products, the registrant provided the EPA with study data that show that throughout the first 30 days of use, a collar may release as much as 2.9 mg/day of flumethrin (Table 6.2.a on page 22 of the Human Health Risk Assessment). Per the evidence below, this daily release of active ingredient is expected to result in transfer into the home environment and then transport to the sanitary sewer through activities such as handwashing and laundering.

The Human Health Assessment Scoping Document (page 6) notes that no transferable residue study was submitted by the registrant. The preliminary work plan includes a call for data regarding residue transfer to residents, with the testing to include both active ingredients. Such a residue transport study may provide insight about transport of topical pet treatments to consumers and within their homes.

Prior studies have examined the transport of active ingredients from pet collars onto surfaces, such as human hands, that are subsequently washed. One such study quantified glove transfer of tetrachlorvinphos from pet collars.[5] We understand that the EPA team reviewing tetrachlorvinphos (EPA-HQ-OPP-2008-0316) has examined this paper and is planning to use the glove residue data following feedback from the EPA's Human Subjects Review Board.[6]

While a topical spot on, rather than a collar, a 2012 study by Bigelow Dyk et al. presents additional evidence of transport of a topical pet treatment onto human hands and through homes.[7] In the study, researchers monitored transfer of fipronil (from a commercially available

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[1] A BACWA market review identified the following active ingredients in topical pet flea and tick control products: cyphenothrin, deltamethrin, etofenprox, fipronil, flumethrin, imidacloprid, indoxacarb, S-methoprene, pyriproxyfen, permethrin, selamectin, spinetoram and tetrachlorvinphos.

[2] US Census Bureau (2016). American Fact Finder. Monthly Population Estimates for the United States: April 1, 2010 to December 1, 2016. July 1 2015 Population Estimate, US resident population.

[3] Puro G. (2015) Packaged Facts: Pet Medications in the US, 4th Edition.

[4] Sadaria, A.M. (2016). Passage of Fiproles and Imidacloprid from Urban Pest Control Uses Through Wastewater Treatment Plants in Northern California. *Environmental Toxicology and Chemistry*. (In press).

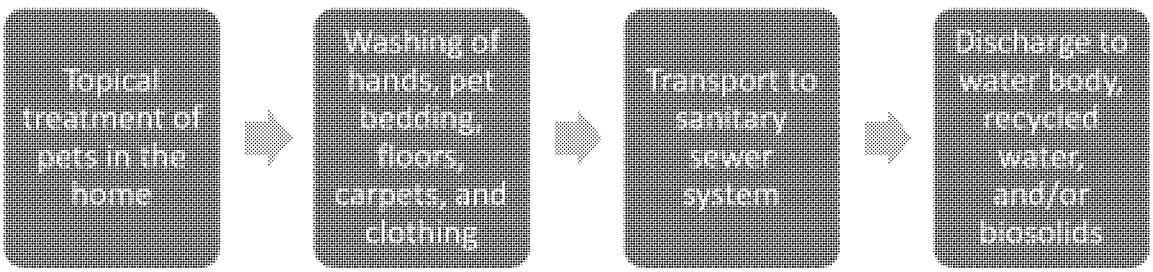
[5] Davis, M., et al. (2008). "Assessing Intermittent Pesticide Exposure From Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos," *J. of Exposure Science and Environ. Epidemiology* **18:**564-570.

[6] https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0316-0040

[7] Bigelow Dyk, M., et al. (2012) Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments, *Journal of Environmental Science and Health, Part B: Pesticides,*

spot-on product) onto pet owners' hands and within their homes over a four-week period following spot treatment application. Participants used cotton gloves to pet their dog or cat for 2 minutes at a time at specific intervals after the application (24 hours, 1 week, 2 weeks, 3 weeks, and 4 weeks). Participants also wore cotton socks for 2 hours a night for 7 nights in a row, for four consecutive weeks following application. The gloves, socks, and brushed pet hair were subsequently analyzed for fipronil and degradates. Bigelow Dyk and colleagues also incorporated a fluorescent dye into the spot treatment to provide photographic evidence of spot-on pesticide transfer. The photographic results shown in the paper illustrate the transfer from the application location to other areas of the pet's fur and onto the pet owners' hands.

These data characterize the first crucial step in the pathway by which topical pet applications can be transported within a home to an indoor drain that flows to a POTW (see graphic).




Further insights regarding transport of indoor flea control products to POTWs comes from a collaborative study of fipronil and imidacloprid (the other active ingredient in the pet collar registration considered in this work plan) at eight POTWs that was recently conducted by the San Francisco Bay Regional Monitoring Program in collaboration with California Department of Pesticide Regulation and Arizona State University (see Attachments 1 and 1a).[8] The study monitored imidacloprid and fipronil, as well as its degradates, in the influent and effluent of eight urban California POTWs. The results indicated that fipronil, its degradates, and imidacloprid were ubiquitous in the influent sewage and final treated effluent of all eight participating POTWs, and suggested that topical pet products may be the primary source of both chemicals in wastewater. Based on the data from Bigelow Dyk and colleagues characterizing topical flea control active ingredient transfer to owners' hands[9] and per capita pet population data, owner handwashing could potentially explain the entire influent load of POTWs sampled in this study;[10] however, pet washing is also a likely discharge pathway.[11]

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*Food Contaminants, and Agricultural Wastes*, **47**(10): 913-924

[8] Sadaria, A.M. (2016). Passage of Fiproles and Imidacloprid from Urban Pest Control Uses Through Wastewater Treatment Plants in Northern California. *Environmental Toxicology and Chemistry.*

[9] Bigelow Dyk, M., et al. (2012) Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments, *Journal of Environmental Science and Health, Part B: Pesticides, Food Contaminants, and Agricultural Wastes*, **47**(10): 913-924

[10] Sadaria, A.M. (2016). Passage of Fiproles and Imidacloprid from Urban Pest Control Uses Through Wastewater Treatment Plants in Northern California. *Environmental Toxicology and Chemistry.* (In press).

[11] Judson, L. et al. (2016). "The Washoff Potential of Fipronil from Dogs Treated with Fipronil Pet-Care Products." Poster presentation, NorCal SETAC, April 27, Oakland CA.

**Estimating Discharges to the Sanitary Sewer from Topical Flea Treatments**

Now that there is evidence of a pathway from this indoor use to a sanitary sewer, EPA needs to consider how to estimate such discharges. One straightforward option—simpler than attempting to estimate transfer coefficients for each transport pathway—would be to estimate the pet flea control transfer fraction on a per capita basis from EPA's proprietary sales data and the Sadaria et al. (2016) per capita POTW influent load data. This would best be done using sales estimates for the Sadaria et al. study location and time period (i.e., San Francisco Bay area, September 2015). A ratio calculated in this manner would amount to a generic estimate of the fraction of topical pet flea control active ingredient ultimately discharged to the sewer. This fraction could be used as a gross estimate of the fractional discharge of other similarly applied topical pet active ingredients.

**Wastewater Discharge ("Down-the-Drain") Modeling Refinements**

Because 100% of POTWs must comply with the Federal Clean Water Act 100% of the time, it is imperative to avoid underestimating pesticide discharge risks. To do so includes addressing both fresh and salt water discharges and modeling of a reasonable worst case – not average conditions.

U.S. EPA OPP uses the "down-the-drain" module from the E-FAST model to estimate surface water concentrations associated with wastewater pesticide discharges. BACWA recommends the following refinement for the modeling of indoor use of spot-on treatments and transport through a sanitary sewer to a water body:

1) Adjust consumer product discharge estimates to reflect geographic and seasonal use
2) Update per capita water use to account for conservation
3) Assume zero dilution
4) Improve POTW removal estimates
5) For pesticides likely to partition to sediment, include a biosolids analysis

These modeling recommendations are further clarified in the appendix.

**BACWA Requests that EPA Complete an Ecological Risk Assessment and that EPA Obtain the Aquatic Toxicity and Environmental Fate Data Necessary for a Quantitative Assessment**

While not specific to flumethrin, the San Francisco Bay Regional Monitoring Program study provides proof that pathways to the sanitary sewer exist for topical pet products, and therefore require an ecological risk assessment. U.S. EPA's preliminary work plan does not propose to include an ecological risk assessment because these are considered indoor uses. According to the preliminary work plan (emphasis added):

> *"The labeled use and application method of flumethrin limit direct or indirect exposure to outdoor terrestrial areas given that the majority of animals treated primarily reside indoors. ... In addition, the pet collar use of flumethrin* ***is unlikely to result in exposure to aquatic resources*** *or groundwater as any solubilized material will be diluted as well. ...* ***risks to non-target organisms are not expected*** *due to the low exposure potential." (Draft Work Plan, page 7).*

In a parallel explanation, the endangered and threatened species assessment of the preliminary work plan included a No Effect (NE) determination for all listed species.

While this assumption has been standard practice for OPP,[12] now that scientific data have demonstrated that aquatic exposures from topical pet treatments are not de minimis, BACWA requests that EPA revise its work plan to include an ecological risk assessment that evaluates sewer discharge-related risks from such pet treatments. If significant risks are identified, we request that U.S. EPA OPP consider risk mitigation options.

In addition, as noted in the preliminary work plan, "there are currently no toxicity data to assess the potential risk to other terrestrial or aquatic organisms from the registered use of flumethrin." Therefore, BACWA requests that the Final Work Plan include a call for toxicity data for aquatic organisms (freshwater and marine) and all environmental fate data necessary to complete a quantitative risk assessment in the Data Needs Table (Table 1, page 4).

**BACWA Requests Benefits Assessment Consider Alternatives to Topical Insecticides for Pet Flea Control**

Since FIFRA is a risk-benefit statute, OPP is required to consider risk mitigation options in the context of the benefits of pesticide use. BACWA requests that for pet flea control products, OPP conduct this examination in the context of available non-pesticide alternatives. Although topical pet products currently dominate the flea control market, new pill form products have recently become available. The new pills, which are registered by FDA rather than EPA, appear to eliminate aquatic (and human) exposure pathways and should be equally or more convenient for pet owners, once they have obtained a prescription from a veterinarian. The involvement of the veterinarian has the added benefit of providing pet-specific guidance on flea control approach and safe dosage. Non-pesticide mechanical controls, such as frequent indoor vacuuming and washing of pet bedding are another alternative (and may be key to effectively overcoming any flea infestation),[13] because the fleas found on one's pet are estimated to represent only 1-5% of the flea cycle in a home; the other 95% are found as eggs, larvae, pupae, and adult fleas throughout the home and surrounding environment.[14]

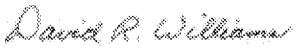
Thank you for your consideration of our comments. If you have any questions, please contact BACWA's Project Managers:

Karin North
City of Palo Alto
(650) 329-2104
Karin.north@cityofpaloaloalto.org

Melody LaBella
Central Contra Costa Sanitary District
(925) 229-7370
mlabella@centralsan.org.

[12] BACWA teleconference meeting with Pesticide Reevaluation Division, Environmental Fate and Effects Division, and Biological and Economic Analysis Division staff, January 20, 2016.
[13] American Veterinary Medical Association (2009). External Parasites.
[14] Halos, L., et al. (2014). Flea Control Failure? Myths and Realities. *Trends in Parasitology*, **30**:5 228-233.

Respectfully Submitted,



David R. Williams
Executive Director
Bay Area Clean Water Agencies

Enclosures:

1. Sadaria, A.M. et al. (2016). Passage of Fiproles and Imidacloprid from Urban Pest Control Uses Through Wastewater Treatment Plants in Northern California. *Environmental Toxicology and Chemistry*. (In press).
2. Bigelow Dyk, M. et al. (2012). Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments, *Journal of Environmental Science and Health, Part B: Pesticides, Food Contaminants, and Agricultural Wastes*, **47**(10): 913-924
3. Halos, L. et al. (2014). Flea Control Failure? Myths and Realities. *Trends in Parasitology*, **30**:5 228-233.

cc: Yu-Ting Guilaran, Director, Pesticide Re-Evaluation Division
Jack Housenger, Director, EPA Office of Pesticide Programs
Tracy Perry, EPA OPP Pesticide Re-Evaluation Division
Rick P. Keigwin, Jr., Deputy Office Director for Programs, EPA OPP
Kevin Costello, Branch Chief, EPA OPP, Pesticide Re-Evaluation Division
Linda Arrington, Branch Chief
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Thomas Steeger, Ph.D., Senior Science Advisor, EFED
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Garland Waleko, Pesticide Re-Evaluation Division, EPA OPP
Andrew Sawyers, Director, EPA Office of Water, Office of Wastewater Management
Tomas Torres, Director, Water Division, EPA Region 9
Debra Denton, EPA Region 9
Patti TenBrook, EPA Region 9
Dawit Tadesse, California State Water Resources Control Board
Noelle Patterson, California State Water Resources Control Board
Tom Mumley, California Regional Water Quality Control Board, SF Bay Region
Janet O'Hara, California Regional Water Quality Control Board, SF Bay Region
James Parrish, California Regional Water Quality Control Board, SF Bay Region
George Farnsworth, Associate Director, California Department of Pesticide Regulation
Nan Singhasemanon, California Department of Pesticide Regulation
Jennifer Teerlink, California Department of Pesticide Regulation
Kelly D. Moran, Urban Pesticides Pollution Prevention Partnership
Chris Hornback, Chief Technical Officer, National Association of Clean Water Agencies
Cynthia Finley, Director, Regulatory Affairs, National Association of Clean Water Agencies
BACWA Executive Board

## Appendix: Wastewater Discharge ("Down-the-Drain") Modeling Refinements

BACWA recommends the following refinement for the modeling of indoor use of topical treatments and transport through a sanitary sewer to a water body:

1) Adjust consumer product discharge estimates to reflect geographic and seasonal use
2) Update per capita water use to reflect today's conditions and account for conservation
3) Assume zero dilution
4) Improve POTW removal estimates
5) For pesticides likely to partition to sediment, include a biosolids analysis

### 1) Adjust Consumer Product Discharge Estimates to Reflect Geographic and Seasonal Use

For the discharge of consumer products to a sewer, the default approach for the E-FAST down-the-drain (DTD) model involves assuming 100% discharge of the annual manufacturing production volume of the chemical and equal discharge throughout all US households. While this approach could be useful for screening purposes, it is unreasonable for many categories of products. In the case of flea control products, usage is not consistent throughout the year or across the nation, as flea pressure differs based on geography and by season. For example, flea pressure is low during freezing winters and highest in late summer. Geographic areas with climates most conducive to flea reproduction (e.g., mild weather coastal areas) experience the highest flea pressure. And, while veterinarians typically recommend regular use of topical treatments, consumers often seek treatments upon identifying a flea outbreak.

### 2) Update Per Capita Water Use to Account for Conservation

The overall daily water use in a household dilutes the concentration of chemicals entering the sanitary sewer. The water use default in the E-FAST DTD model appears to be significantly greater than currently-observed per capita water use in many of the nation's urban areas. Particularly in regions of the US that are impacted by drought, the influent flow volume to POTWs has reduced significantly since the 1990s, due to conservation, national and state code requirements for installation of low-flow toilets and showerheads, and new high-efficiency washing machines (see table). BACWA recommends that U.S. EPA consider using 5th or 10th percentile per capita flows to be sufficiently conservative in the model analysis.

| Location | Per Capita Daily Water Use (Liters) | Source |
|---|---|---|
| E-FAST DTD Model | 364 (original)<br>388 (current) | 1990 and 1996 U.S. EPA POTW surveys[15] |
| California, January 2016 (includes outdoor uses) | 230 (statewide)<br><190 (many cities) | California State Water Board[16] |
| Texas, 2012 | 230 | Texas Water Development Board[17] |

[15] Versar (1999). Exposure and Fate Assessment Screening Tool (E-FAST) Beta Version Documentation Manual prepared for U.S EPA OPPTS; Versar (2007). Exposure and Fate Assessment Screening Tool (E-FAST) Version 2.0 Documentation Manual. Prepared for U.S. EPA OPPTS.
[16] California water usage data are available online: http://www.waterboards.ca.gov/water_issues/programs/conservation_portal/conservation_reporting.shtml January data, which are during the rainy season in California's Mediterranean climate and thus reflect minimal outdoor water use, are typically used to estimate indoor water use and wastewater discharges.
[17] Hermitte, S.M. and Mace, R.E. (2012). *The Grass Is Always Greener…Outdoor Residential Water Use in Texas*. Texas Water Development Board, Technical Note 12-01.

**3) Assume Zero Dilution**

The E-FAST model manual notes that a range of dilution factors may be employed when analyzing POTW impacts to receiving waters: "Measured dilution factors are typically between 1 (representing no dilution) and 200 and are based on NPDES permits or regulatory policy."[18] BACWA recommends that the spot-on modeling analysis assume no dilution.

In California, approximately 20 percent of NPDES permits provide for no dilution. Throughout the US, about 23 percent of POTWs have a permitted dilution factor less than 10. Further, treated wastewater effluent makes up more than 90 percent of stream flow for 49 percent of a representative sample of major POTWs in Texas, Oklahoma, New Mexico, Arkansas, and Louisiana.[19] In the case of multiple sanitary sewer systems and/or urban and agricultural runoff discharging into the same water body, the "diluting" waters may also contain the pollutant.

**4) Improve POTW Removal Estimates**

Because there is variety in POTW treatment trains, with different types and levels of treatment, and different detention times, pesticide removal rates are expected to vary from facility to facility. Rather than use an average removal rate, consider using a range of removal rates to determine whether certain treatment trains might be more at risk of permit violation. Because it is unlikely that POTWs currently have influent and effluent data for flumethrin, one approach would be to use the EPI Suite model, as a predictive tool of percent removal, developed by the Office of Pollution Prevention and Toxic Risk Assessment Division and Syracuse Research Corporation.

**5) For Pesticides Likely to Partition to Sediment, Include a Biosolids Analysis**

Given the low volatility and the octanol-water coefficient for flumethrin, it is likely to partition into sediment. Therefore BACWA requests that U.S. EPA include an evaluation of the adsorption and partitioning to the POTW biosolids. The E-FAST DTD model assumes that the biosolids (referred to as "sludge") are landfilled. This assumption does not reflect the routine use of biosolids as a soil amendment in agriculture, gardens, parks and reclamation sites. POTWs have come to consider biosolids to be valuable resource. It is important to understand how the partitioning of industrial insecticides into biosolids could impact the value and end uses of this resource.

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[18] Versar (2007). Exposure and Fate Assessment Screening Tool (E-FAST) Version 2.0 Documentation Manual. Prepared for U.S. EPA OPPTS. Page 3-33.

[19] Brooks et al. (2006). Water quality of effluent-dominated ecosystems: ecotoxicological, hydrological, and management considerations. *Hydrobiologia* **556:**365–379

SETAC PRESS

Environmental Toxicology and Chemistry, Vol. 9999, No. 9999, pp. 1–10, 2016
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Printed in the USA

*Environmental Chemistry*

# PASSAGE OF FIPROLES AND IMIDACLOPRID FROM URBAN PEST CONTROL USES THROUGH WASTEWATER TREATMENT PLANTS IN NORTHERN CALIFORNIA, USA

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*(Submitted 19 May 2016; Returned for Revision 22 July 2016; Accepted 1 November 2016)*

**Abstract:** Urban pest control insecticides—specifically fipronil and its 4 major degradates (fipronil sulfone, sulfide, desulfinyl, and amide), as well as imidacloprid—were monitored during drought conditions in 8 San Francisco Bay (San Francisco, CA, USA) wastewater treatment plants (WWTPs). In influent and effluent, ubiquitous detections were obtained in units of ng/L for fipronil (13–88 ng/L), fipronil sulfone (1–28 ng/L), fipronil sulfide (1–5 ng/L), and imidacloprid (58–306 ng/L). Partitioning was also investigated; in influent, 100% of imidacloprid and 62 ± 9% of total fiproles (fipronil and degradates) were present in the dissolved state, with the balance being bound to filter-removable particulates. Targeted insecticides persisted during wastewater treatment, regardless of treatment technology utilized (imidacloprid: 93 ± 17%; total fiproles: 65 ± 11% remaining), with partitioning into sludge (3.7–151.1 μg/kg dry wt as fipronil) accounting for minor losses of total fiproles entering WWTPs. The load of total fiproles was fairly consistent across the facilities but fiprole speciation varied. This first regional study on fiprole and imidacloprid occurrences in raw and treated California sewage revealed ubiquity and marked persistence to conventional treatment of both phenylpyrazole and neonicotinoid compounds. Flea and tick control agents for pets are identified as potential sources of pesticides in sewage meriting further investigation and inclusion in chemical-specific risk assessments. *Environ Toxicol Chem* 2016;9999:1–10. © 2016 SETAC

**Keywords:** Insecticide  Water quality  Persistant organic pollutants (POPs)  Fate and transport  Pesticides

## INTRODUCTION

Over the last decade, 2 newer insecticides, fipronil and imidacloprid, have gradually replaced older active ingredients in common urban pest control applications, such as pet flea treatments and professional insect control products [1,2]. The phase-out of most organophosphate insecticides for urban uses in the early 2000s opened markets that soon were filled by fipronil and imidacloprid formulations. Continued growth of urban uses is likely in the present decade in large part because of the replacement of pyrethroids, an older class of insecticides that are widely detected in urban streams and have come under scrutiny for adverse impacts on the health of aquatic invertebrates [3–6], findings that triggered federal and state regulatory responses [7,8]. Fipronil, a phenylpyrazole insecticide, has multiple urban uses including sprays for the outdoor perimeter of buildings to control ants and other insects, underground injections to control termites, pet treatments for fleas and ticks, gels for crack and crevice treatment, insect control baits, and, except in California, landscape maintenance [1,9,10]. Imidacloprid, a neonicotinoid insecticide, has urban applications in lawn and landscape maintenance, outdoor structural pest control, indoor bedbug and nuisance insect control, underground injections to control termites, and pet treatments for fleas and ticks [1,11]. Imidacloprid is also used as an insecticidal component of manufactured materials such as polystyrene insulation, vinyl siding, adhesives, sealants, textiles for outdoor uses, and pressure-treated wood decking [11–13].

Both pesticides are toxic to sensitive aquatic invertebrates at low parts-per-trillion concentrations (<100 ng/L) [14,15]. In 2007, the US Environmental Protection Agency (USEPA) established aquatic life benchmarks for fipronil (11 ng/L), as well as its degradates fipronil sulfone (37 ng/L), fipronil sulfide (110 ng/L), and fipronil desulfinyl (590 ng/L) based on chronic exposure studies of multiple freshwater invertebrates [16]. Recently published invertebrate toxicity data [15] show chronic effects to aquatic invertebrates at concentrations of 7 ng/L to 8 ng/L for fipronil sulfone and 9 ng/L to 11 ng/L for fipronil sulfide, lower than the USEPA's 2007 benchmarks. Fish appear to be less sensitive to fipronil and its degradates; USEPA chronic aquatic life benchmarks for freshwater fish range from 6600 ng/L for fipronil to 590 ng/L for fipronil desulfinyl [16]. In 2008, the USEPA established an aquatic life benchmark of 1050 ng/L for imidacloprid based on chronic exposure studies of *Daphnia magna* [11]. However, a recent summary of chronic toxicity data indicates that mayflies can experience effects such as immobilization after long-term exposure at concentrations of less than 100 ng/L and that the majority of other invertebrates studied are 100 to 1000 times more sensitive to imidacloprid than *D. magna* [14]. A more recent evaluation by the European Union of imidacloprid toxicity data [17] has established a predicted no-effect concentration (PNEC) of 4.8 ng/L; this was based on species sensitivity distribution information incorporating recent toxicity data, such as the mayfly nymph immobilization effective concentration, 10% (EC10) value of approximately 30 ng/L [18]. Fish are less sensitive to

This article includes online-only Supplemental Data.
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Published online 3 November 2016 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/etc.3673



ED_002155A_00006478-00009

imidacloprid, as evidenced by the USEPA fish chronic benchmark of 1.2 mg/L [11].

Both fipronil and imidacloprid are commonly detected in urban streams [6,19,20]. For example, a survey of storm drains in California found median levels of fipronil to be 33 ng/L in northern California and 76 ng/L in southern California; fipronil sulfone (medians of 26 ng/L and 77 ng/L for northern and southern California, respectively) and fipronil desulfinyl (medians of 15 ng/L and 41 ng/L for northern and southern California, respectively) were also frequently detected [6,19]. Another California survey of urban surface waters measured maximum imidacloprid levels of 160 ng/L during the dry season and 670 ng/L during the wet season [6].

For both of these pesticides, relatively few data are available concerning levels in urban wastewater before and after treatment. This data gap also exists for treated and untreated wastewater sludge, despite ubiquitous urban application of these pesticides, as well as the demonstrated presence of another group of popular urban insecticides, the pyrethroids, in treated wastewater and biosolids [21]. Fipronil has been detected in treated wastewater discharged by 9 of 25 US wastewater treatment plants (WWTPs; <10–70 ng/L) [22]; 6 Florida WWTPs (16–110 ng/L) [23]; 7 of 9 Oregon and Washington municipal WWTPs (27–130 ng/L) [24]; 2 California WWTPs (<1–57 ng/L) [15]; and 1 southwestern US WWTP (13–21 ng/L) [25]. Some of the facilities studied thus far treat a mixture of wastewater and urban runoff (California, 1; Florida, 6). Past measurements of influent and effluent suggested little if any removal of fipronil during typical wastewater treatment [15,22,23,25]. However, prior studies were sometimes limited by featuring approximately 2- to 50-fold higher method detection limits, failing to monitor all major fipronil transformation products, or omitting analysis of suspended particulates that were removed by filtration or other treatment prior to analysis [15,22,23,25]. Presently available and still limited data on fipronil degradates suggest sporadic, low-level occurrence of fipronil desulfinyl [15,23,24], as well as fipronil sulfone, sulfide, and amide [25], in wastewater treatment flows. Fipronil and its degradates were also detected in 2 effluent-dominated rivers in southern California during low flow conditions [26]. Available data suggest that concentrations of fipronil in treated effluent frequently approach or exceed USEPA chronic invertebrate aquatic life benchmark [25,26].

Fipronil and its degradates, jointly referred to as total fiproles, feature logarithmic octanol–water partitioning coefficient ($\log K_{OW}$) values > 4. This characteristic enables them to sorb to particles in wastewater that settle during treatment, ultimately leading to a sequestration of fipronil-related compounds in sewage sludge and treated sludge deemed fit for application on land (biosolids). Two studies have reported measurable concentrations of fipronil and degradates in this matrix [22,25].

Likewise, few studies have examined imidacloprid in municipal wastewater. Imidacloprid was detected in <10% of treated effluent samples from 52 Oregon municipal WWTPs (202–387 ng/L), using a higher method detection limit of 200 ng/L; influent and biosolids were not sampled [27]. To date, there are no published studies reporting on measured imidacloprid levels in biosolids, possibly because the low log $K_{OW}$ value of imidacloprid (<1) does not suggest partitioning into sludge as an important process. Studies of imidacloprid in wastewater in China and Spain (where allowable uses may differ from those in the United States) suggest that typical treatment technologies may result in low removal of imidacloprid from the liquid phase prior to discharge into receiving waters [28,29]. A study of an effluent-dominated waterway in Iowa indicated that treated wastewater can introduce imidacloprid to receiving waters [20].

In the present study, we explored the presence of fipronil, its 4 major degradates, and imidacloprid in urban wastewater before and after treatment, providing the first regional set of data for WWTPs across varying treatment technologies. Furthermore, to add to still limited literature data, we also analyzed sludges from the sampled plants for insecticide occurrence. Finally, we assessed sources related to urban uses of these pesticides.

## MATERIALS AND METHODS

### *Standards and reagents*

High-performance liquid chromatography (HPLC)–grade organic solvents (methanol, acetone, methylene chloride, and hexane) and water were purchased from Sigma-Aldrich and Thermo Fisher Scientific, respectively. Analytical standards of imidacloprid, fipronil, fipronil desulfinyl, and deuterated labeled standard [$d_4$] imidacloprid were obtained from Sigma-Aldrich. Analytical standards of fipronil sulfide, sulfone, and amide were obtained from Bayer and BASF. Labeled [$^{13}C_2{}^{15}N_2$] fipronil and [$^{13}C_4{}^{15}N_2$] fipronil sulfone were bought from Toronto Research Chemicals and Cambridge Isotope Laboratories, respectively. Stock solutions of analytical standards were prepared in acetonitrile and stored at –20 °C.

### *Sample collection*

Single 24-h composite samples of influent and effluent were collected from each of 8 facilities that discharge to San Francisco Bay (San Francisco, CA, USA). Facilities that provided samples were selected based on multiple factors, including higher discharge levels, geographic diversity, and range of treatment technologies (secondary only vs tertiary filtration; Table 1). As a consequence of drought-related water use restrictions, facilities were operating well below capacities (Table 1). One facility sampled serves only a large airport and the associated operations. The remaining 7 locations, representative of more typical municipal WWTPs, had per capita daily influent flows of 235 L/person/d to 302 L/person/d. Autosamplers at all facilities provided flow-weighted composite samples, with the exception being the San José–Santa Clara influent compositer, which provides a flow-weighted composite of 6 subsamples collected regularly throughout the 24-h period. Wastewater recycling, including reverse osmosis treatment of <10% of the San José–Santa Clara facility secondary effluent, reduces effluent flow. Reverse osmosis recycling returns a concentrate that is mixed with effluent prior to discharge. The sampling location includes the returned concentrate volume and represents roughly 2% of the total effluent volume.

Influent, effluent, and dewatered/treated sludge samples were collected simultaneously during mid-week of September 2015. The San Francisco Bay region is subject to a mild, Mediterranean climate; September is within the dry season and was selected specifically as an appropriate period of study to avoid rainfall-related inflow and infiltration. Inflow of urban runoff would include fiproles and imidacloprid; by excluding runoff as a potential source, the study design allows specific insight regarding indoor sources. Of note, none of the facilities typically treat storm water. The mild climate in this coastal region also allows fleas to flourish year-round [30], motivating continued residential use of flea control pesticides. Wastewater

Table 1. Characteristics of wastewater treatment plants and processes monitored in the present study

| WWTP | Population served (thousands) | Plant capacity (MGD) | Wastewater treatment: Primary | Secondary | Disinfection | Advanced | Sludge treatment | Influent flow (MGD) | HRT (h) | TSS (mg/L): Inf | Eff |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SFTP | [a] | 2.2 | PS | SBR | Cl2 | — | AD | 0.45 | 5.75 | 1004 | 20 |
| PARP | 220 | 39 | PS | FFR, AS | UV | F | NT | 16.86 | 22 | 322 | <1 |
| SJSC | 1400 | 167 | PS | AS | Cl2 | F | AD | 92.76 | 9 | 315 | 1 |
| SLWP | 55 | 7.6 | PS | FFR, AS | Cl2 | — | AD | 4.15 | 10 | 517 | 9 |
| SMWP | 140 | 15 | PS | AS | Cl2 | F | AD | 9.02 | 14.6 | 414 | 9 |
| EBMUD | 650 | 120 | PS | AS | Cl2 | — | AD | 45.00 | 15 | 340 | 11 |
| FSSD | 139 | 23.7 | PS | AS | UV | F | AD | 11.21 | 24 | 237 | <1 |
| CCSD | 471 | 53.8 | PA, PS | AS | UV | — | NT | 29.27 | 6.5 | 312 | 8 |

[a]Annually, 56 million people pass through airport facilities.
WWTP = wastewater treatment plant; MGD = million gallons per day; HRT = hydraulic retention time; TSS = total suspended solids; Inf = influent; Eff = effluent; SFTP = San Francisco International Airport Commission Mel Leong Treatment Plant; PARP = City of Palo Alto Regional Water Quality Control Plant; SJSC = San Jose-Santa Clara Regional Wastewater Facility; SLWP = San Leandro Water Pollution Control Plant; SMWP = City of San Mateo Waste Water Treatment Plant; EBMUD = East Bay Municipal Utility District Wastewater Treatment Plant; FSSD = Fairfield-Suisun Sewer District Wastewater Treatment Plant; CCSD = Central Contra Costa County Sanitary District Treatment Plant; PS = primary sedimentation; PA = pre-aeration; SBR = sequential batch reactor; FFR = fixed film reactor; AS = activated sludge; Cl2 = chlorine disinfection; UV = ultraviolet disinfection; F = filtration; AD = anaerobic digestion; NT = no treatment;

samples were collected in 2-L amber glass jars to which the biocide Kathon CG/ICP (for more information see the Supplemental Data) and sodium thiosulfate were added for disinfection and preservation. Sludge samples were collected in 0.5-L amber glass jars. Wastewater samples were refrigerated at 4 °C and analyzed within 10 d of collection, and sludge samples were stored at –20 °C until extraction.

*Extraction of influent solid and biosolids samples.*

Wastewater influent was separated into aqueous phase and particulates and analyzed separately to determine the distribution and total mass loading of pesticides entering the WWTPs. For this purpose, influent samples were centrifuged at 3000 *g* for 5 min, and settled particulates were dried under a gentle stream of nitrogen. Analyte extraction of solids from influent and of biosolids was performed using established protocols [25,31]. One gram of nitrogen-dried solid sample was spiked with 20 ng of labeled [$^{13}C_2{}^{15}N_2$] fipronil, [$^{13}C_4{}^{15}N_2$] fipronil sulfone, and 200 ng of labeled [$d_4$] imidacloprid, extracted with 10 mL acetone, twice, by 24 h of shaking, followed by 1 h of sonication. Later, extracts were centrifuged, supernatants were nitrogen-dried and reconstituted to 2 mL hexane, and Florisil cleanup (solid-phase extraction with a sorbent bed containing mixture of magnesium oxide and silica gel) was performed. Analytes were eluted successively from a Florisil cartridge (Sep-Pak Vac Florisil Cartridge 6 cc containing 1 g of sorbent; Waters) with 4 mL methylene chloride and 4 mL acetone. Later, 1 mL of each extract was mixed, evaporated with nitrogen, and reconstituted to 1 mL of water and methanol solution (50:50, v/v) for fipronil and its degradates (sulfone, sulfide, and amide). Similarly, extracts were mixed, dried, and reconstituted to 1 mL of hexane for fipronil desulfinyl, and 1 mL of water, methanol, and formic acid solution (80:20:0.1, v/v/v) for imidacloprid analysis.

*Extraction of wastewater samples*

The wastewater extraction protocol was similar to that described in previous studies [25,31]. First, 20 ng of labeled [$^{13}C_2{}^{15}N_2$] fipronil and [$^{13}C_4{}^{15}N_2$] fipronil sulfone, and 200 ng of labeled [$d_4$] imidacloprid were spiked to a 500-mL wastewater sample. Later, samples were loaded on a cartridge having reverse-phase functionalized polymeric styrene divinylbenzene sorbent (Strata X & XL, 500 mg/3 mL; Phenomenex) using an automatic solid-phase extraction instrument (Dionex AutoTrace 280; Thermo Scientific) at a constant flow rate of 2 mL/min. Cartridges were eluted with 8 mL of methanol and formic acid mixture (95:5, v/v). Extracts were dried and reconstituted similarly to solid samples and prepared for analysis by chromatography separation and tandem mass spectrometry (MS/MS).

*Chromatography separation and MS/MS*

Imidacloprid, fipronil, and degradates, except for fipronil desulfinyl, were separated by liquid chromatography (LC) and detected and quantified by electrospray ionization–MS/MS. Liquid chromatography mass spectrometric analyses were performed using a Shimadzu Prominence HPLC (Shimadzu Scientific) coupled to an ABSciex API-4000 MS/MS (Applied Biosystems). Liquid chromatographic separation was achieved by an XBridge C8-column (3.5-μm particle size, 2.1 mm × 100 mm; Waters). The injection volume was 50 μL. For fipronil and its degradates, the mobile phase consisted of water and methanol at a total flow rate of 0.2 mL/min with a total runtime of 10 min. The binary gradient consisted of 40% methanol with a 5-min ramp of 10% solvent content increase per minute to 95% methanol, where it was held for 3.5 min. For imidacloprid, the mobile phase consisted of 0.1% formic acid in water and methanol at a total flow rate of 0.2 mL/min with a total run time of 12 min. The binary gradient consisted of 20% methanol with a 6-min ramp of 16.7% solvent content increase per minute to 95% methanol, where it was held for 3.5 min. The electrospray ionization probe was operated in negative mode for fipronil and its degradates, and in positive mode for imidacloprid. Multiple reaction monitoring was used for qualitative analysis. Fipronil desulfinyl was analyzed using gas chromatography–electron impact–MS/MS because it exhibited a considerably lower detection limit than LC–MS/MS (see the Supplemental Data).

*Quality assurance and quality control*

For every 5 samples analyzed, 1 method blank was included in the analytical batch. Matrix spike and matrix spike duplicates were performed at a frequency of 1-in-4 and 1-in-6 for wastewater and solids, respectively. Replicate analyses were

performed at a frequency of 1-in-3 and 1-in-5 for wastewater and solids, respectively, to determine relative percentage deviation. Field duplicates (blind samples) were also collected and analyzed for all analytes for quality assurance. Every shipment of samples included 1 field/trip blank to judge the integrity of sample handling and shipping.

*Method performance*

The MS/MS method targeted analytes by monitoring 2 ion transitions. Mass spectrometry parameters optimized for multiple reaction monitoring are provided in Supplemental Data, Table S1. Method detection limits of analytes in wastewater ranged from 0.1 ng/L to 0.8 ng/L and in sewage particulates from 0.1 μg/kg to 1.1 μg/kg dry weight (Supplemental Data, Table S2) [25,31]. Relative percentage difference values determined for the studied analytes in samples and in the corresponding duplicates (laboratory and field duplicates) averaged $11 \pm 12\%$. Absolute recoveries (average ± standard deviation) of analytes in all matrix spike and matrix spike duplicate samples were $58 \pm 30\%$, and relative recoveries (isotope-corrected) were $98 \pm 10\%$. Field blanks and method blanks (included to monitor for postsample collection contamination) showed no detectable levels of analytes.

## RESULTS AND DISCUSSION

*Detection of fipronil and its degradates in wastewater treatment streams*

Fipronil, fipronil sulfone, and fipronil sulfide were detected with 100% detection frequency in all influent and effluent samples of 8 WWTPs analyzed (Figure 1; Supplemental Data, Tables S3 and S4). Fipronil amide, a product of fipronil hydrolysis, was absent in all influent samples (<0.3 ng/L), but was detected in effluent samples of 7 of 8 WWTPs, suggesting that hydrolysis took place primarily during biological treatment. The photolysis degradate, fipronil desulfinyl, was detected only in a single WWTP, in both influent and effluent. In this and 2 additional WWTPs, ultraviolet disinfection was performed but it did not lead to increase in the photolysis degradate. In all WWTPs examined, fipronil and fipronil sulfone were the most prevalent fiproles by concentration. In the aqueous phase of influent and effluent samples, fipronil concentrations ranged between 8.6 ng/L and 74.9 ng/L and between 14.3 ng/L and 48.6 ng/L, respectively, and fipronil sulfone concentrations ranged between 1.1 ng/L and 11.9 ng/L and between 1.1 ng/L and 16.3 ng/L, respectively. For 6 of the 8 WWTPs studied, sulfone concentration in the effluent was greater than the aqueous phase influent concentration (Figure 1). Fipronil sulfide, amide, and desulfinyl concentrations were less than 5 ng/L. Although the WWTPs studied performed a variety of treatment processes (Table 1), fipronil persistence was roughly comparable across all treatment regimes. Paired *t* test revealed that the total molar concentration of all fipronil-related compounds in aqueous phase influent and effluent at all 8 WWTPs was statistically indistinguishable ($p = 0.95$); however, it should be noted that the sampling strategy was not designed to account for hydraulic retention time (HRT) of treatment trains and instead was meant to yield an average concentration over a 24-h time period.

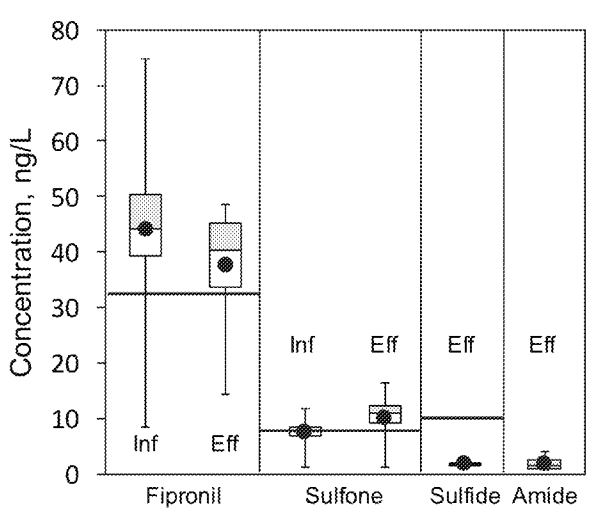


Figure 1. Detected concentrations of fipronil and its degradates (ng/L) in the dissolved phase from 8 wastewater treatment plants in northern California. Red horizontal lines indicate published chronic toxicity values for *Chironomus dilutus*, a freshwater invertebrate [15]. Inf = influent; Eff = effluent.

*Distribution of fipronil and its degradates in wastewater*

Previous studies have analyzed wastewater samples by filtering [15,23] or by analyzing supernatants [22,25]. As fipronil and its degradates have log $K_{OW}$ values >4 (Supplemental Data, Table S2), there may be a considerable mass bound to the particulate fraction, unassessed by previous studies of influent. Among all 8 WWTPs studied, the majority of fipronil ($76 \pm 8\%$ by mass) was present in the aqueous phase (Supplemental Data, Figure S1). For fipronil sulfone, however, $66 \pm 7\%$ of the mass was particulate bound. Fipronil sulfide, the anaerobic degradate, was present in the particulate fractions of all influent samples but was not detected in the aqueous phase (method detection limit = 0.2 ng/L). Of note, the molar distribution of fiproles in the influent phases likely reflects biotransformation in the sewer as well as physical partitioning and potential other, nonhydrophobic interactions. Individual mass distributions of fipronil and its degradates in all influent samples is provided in the Supplemental Data, Table S5. Of the total molar mass of fiproles, $62 \pm 9\%$ was present in the dissolved phase, and a considerable fraction ($38 \pm 9\%$) was particulate bound, which reflects the intermediate log $K_{OW}$ values of fipronil and its degradates. Measured concentrations in different phases of analytes are provided in Supplemental Data, Table S3 and S4. As effluent samples featured low total suspended solids values between <1 mg/L and 20 mg/L, extraction and analysis of particulates from effluent was not feasible; however, considering the low amounts of particulates in treated effluent, calculations suggest that the sorbed mass of fipronil-related compound on effluent particulates was less than 0.75% of the total.

Among all 8 treatment facilities studied, the molar distribution of fipronil and its degradates differed by treatment stream and matrix, but some general trends were consistently seen across all WWTPs investigated (Figure 2). In influent, significant differences in the molar distribution of fipronil and its degradates were evident within the aqueous versus particulate phases. Aqueous phase influent was composed of $86 \pm 3\%$ fipronil and $14 \pm 3\%$ sulfone. In particulates, the molar distributions of fipronil, sulfone, and sulfide were $44 \pm 4\%$, $46 \pm 8\%$, and $9 \pm 8\%$, respectively. Total influent was comprised of $70 \pm 3\%$ fipronil, $26 \pm 4\%$ sulfone, and $4 \pm 4\%$ sulfide. Individual molar distributions for each influent sample are provided in Supplemental Data, Table S5. Discharged effluent, on average, carried fiproles distributed in the following way: $74 \pm 6\%$ fipronil, $18 \pm 6\%$ sulfone, $4 \pm 1\%$ sulfide, $3 \pm 2\%$

Total fiprole loading at 8 wastewater treatment plants in pico-mol/L

| | Fipronil | Sulfone | Sulfide | Amide | Desulfinyl | Total fiproles |
|---|---|---|---|---|---|---|
| Influent - aq phase | 806 | 131 | 0 | 0 | 3 | 940 |
| Influent - particulates | 234 | 251 | 44 | 0 | 0 | 528 |
| Total influent | 1040 | 382 | 44 | 0 | 3 | 1468 |
| Effluent | 690 | 180 | 34 | 28 | 6 | 938 |

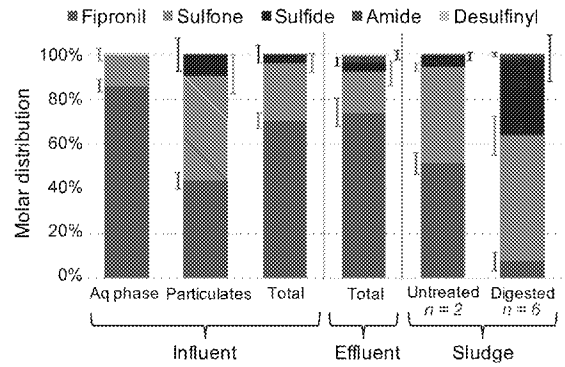


Figure 2. Molar distribution of fipronil and its degradates in treatment streams of 8 wastewater treatment plants. Error bars indicate standard deviation or min/max values when only 2 measurements were available (i.e., for untreated sludge).

amide, and $1 \pm 1\%$ desulfinyl. The small variability observed in the molar distribution in effluent from different treatment plants also suggests that the proportion of the fipronil and its degradates is not strongly influenced by factors such as unit operations, HRT, and sludge age.

*Fate of fipronil and its degradates in wastewater and comparison with previous studies*

On a molar concentration basis, $65 \pm 11\%$ of the sum of fipronil and its degradates entering each facility (considering both aqueous and particulate phases of influent) was measured in effluent. As mentioned earlier, aqueous phase influent contained $62 \pm 9\%$ of the total fiprole loading, also suggesting no significant removal from the aqueous phase during treatment, with reductions largely attributable to fiprole removal via partitioning to settleable particulates from the waste stream.

Detected total concentration (aqueous phase + sorbed phase) of the present study, termed "California 2015," are compared with previous studies in Figure 3. Influent and effluent of the same 8 WWTPs were analyzed by the California Department of Fish and Wildlife's Water Pollution Control Laboratory in fall 2014 at the behest of the Regional Monitoring Program for Water Quality in San Francisco Bay; however, the method of isotope dilution was not employed. Furthermore, neither sludge samples nor imidacloprid were analyzed, and samples were filtered prior to analysis. Therefore, data obtained in the 2014 study do not account for fipronil mass sorbed to wastewater particulates. The corresponding results are listed in Figure 3 as "California 2014," and concentrations detected are provided in Supplemental Data, Table S6. A comparison of concentrations and detection frequency of other studies shows the northern California data to be mostly consistent with those of prior work in different geographic regions (Figure 3). A study in the southwestern United States [25] is excluded from the comparison in Figure 3, as it studied fipronil and its degradates in only a single facility.

*Accumulation of fipronil and its degradates in solids*

Six of 8 treatment facilities performed anaerobic digestion of excess solids to produce treated sludge, whereas the remaining 2 facilities incinerated wastewater sludge after dewatering. The molar distribution of fipronil and its degradates in solids was consistent among WWTPs, but differed between anaerobically digested (biosolids) and untreated sludge (Figure 2). Raw excess sludge had $51 \pm 5\%$ fipronil, $43 \pm 2\%$ sulfone, $5 \pm 2\%$ sulfide, and $1 \pm 1\%$ amide, a molar distribution resembling that observed for influent-borne particulates (Figure 2). In anaerobically digested sludge, the molar distribution was different, with the anaerobic degradate fipronil sulfide accounting for $35 \pm 11\%$ and fipronil for only $8 \pm 4\%$ of all fiproles, indicating biotransformation of fipronil as a result of the treatment. The molar distribution of fipronil sulfone ($56 \pm 9\%$) and amide ($2 \pm 1\%$) was somewhat similar to that of untreated sludge. Individual molar distributions for solids from each WWTP are provided in Supplemental Data, Table S5.

Fipronil (0.2–44.1 μg/kg) and the sulfone (1.6–91 μg/kg) and sulfide (0.7–60.3 μg/kg) degradates were detected with 100% detection frequency, and fipronil amide was detected with 88% detection frequency (Figure 4). In the digested sludge produced by 6 of the 8 WWTPs, concentrations of the fipronil degradates sulfone and sulfide were considerably higher than those of the parent compound; this stands in sharp contrast to the composition of the (undigested) sludges produced in 2 facilities utilizing dewatering and incineration. Fipronil desulfinyl was not detected in any of the sludges. Only 2 prior studies have detected fipronil in sludge or biosolids. One of these studied fipronil only in sludge samples of 25 facilities nationwide [22], and another studied fipronil and its degradates in a single facility performing anaerobic digestion for solids treatment [25]. Detected total fipronil concentrations in these studies ranged between 3 μg/kg and 180 μg/kg, which is comparable to the levels observed in the present study (3.7–151.1 μg/kg as fipronil).

*Detection of imidacloprid in wastewater treatment streams*

Imidacloprid was detected with 100% detection frequency in all influent (58.1–306.1 ng/L) and effluent (83.8–305.2 ng/L) samples and was never detected in any of the sludge samples from the 8 WWTPs examined (Figure 5; Supplemental Data, Table S7). In influent, imidacloprid was only detected in the aqueous phase and was not detected on sewage particulates. Although the WWTPs studied employed different treatment processes (Table 1), the occurrence post-treatment of imidacloprid was a phenomenon extant at all facilities. Although sampling did not account for HRT, effluent concentrations accounted for $93 \pm 17\%$ of the loading arriving at the WWTPs on a concentration basis. Thus, none of the diverse treatment processes sampled was effective at imidacloprid removal.

At the San Francisco Airport WWTP, imidacloprid concentrations in effluent were approximately 3 times higher than influent levels, suggesting inconsistent loading into this facility that provides sanitary services to a major US airport. Alternate explanations could not be supported with available evidence [32]. Higher effluent than influent concentrations were not suggested to result from signal suppression because of matrix effects during the LC–MS/MS detection, as an isotope dilution method was used. Furthermore, proper sample preservation measures were taken, and no rainfall events occurred during the sampling event. Thus, the most likely reason for the observation was inconsistent loading at the treatment facility, particularly given that the sampling strategy was not designed to account for the HRT of the treatment train.

When this facility was excluded from the analysis, a 2-tailed paired $t$ test for the remaining 7 plants revealed that influent and

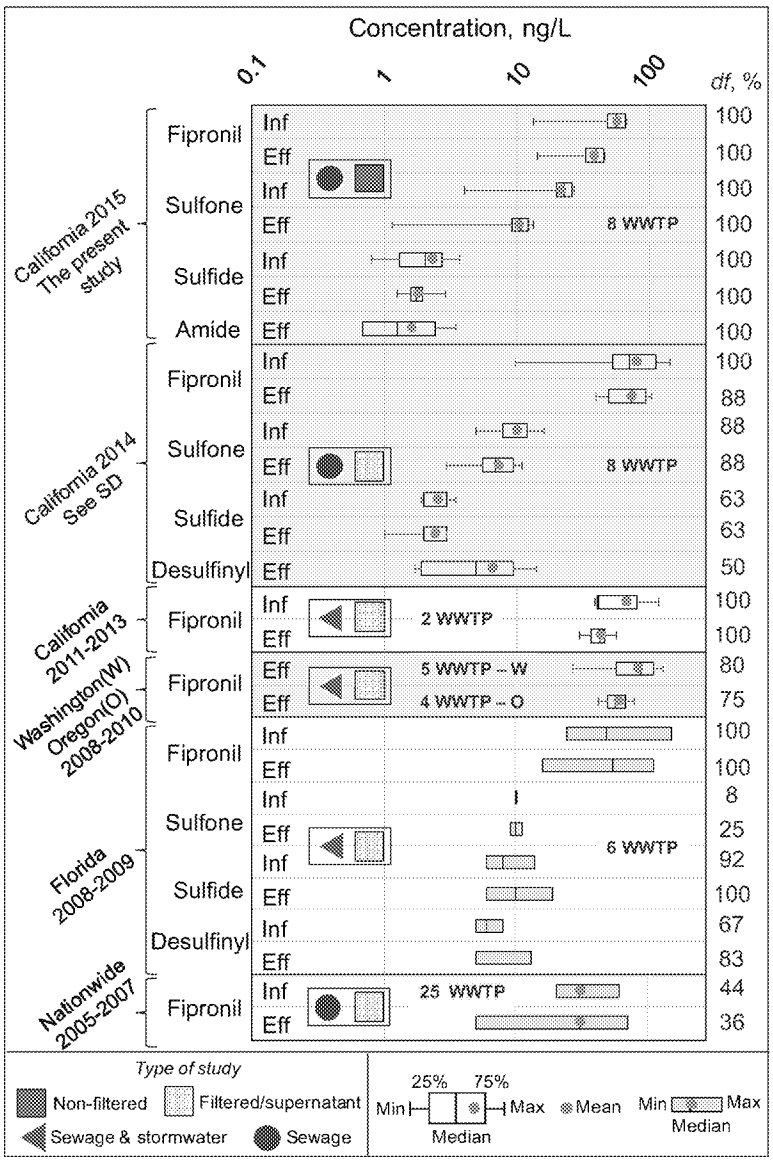


Figure 3. Concentrations of fipronil and its degradates in wastewater samples from 8 California wastewater treatment plants (present study) contrasted with data from past studies [15,22–24]. Years correspond to sampling period. df = detection frequency of compound in process flow; inf = influent; eff = effluent; SD = Supplemental Data.

effluent concentrations were statistically indistinguishable ($p = 0.49$; 95% confidence level), supporting the conclusion of pass-through of imidacloprid.

Levels of imidacloprid in effluent of northern California facilities determined in the present study are generally higher than those observed in a recent assessment of 12 WWTPs from across the United States, which reported a concentration range of 18.5 ng/L to 146.4 ng/L, a dataset included in Figure 5 [31]. An earlier study of effluent from 52 Oregon WWTPs found a relatively low level of detection (9.8% detection frequency);

| WWTP | Fipronil | Sulfone | Sulfide | Amide |
|---|---|---|---|---|
| SFTP | 0.2 | 1.6 | 1.8 | 0.1 |
| *PARP* | *11.4* | *9.0* | *0.7* | *<0.1* |
| SJSC | 0.5 | 9.1 | 4.3 | 0.4 |
| SLWP | 8.8 | 85.0 | 32.3 | 1.0 |
| SMWP | 17.7 | 91.0 | 43.0 | 1.4 |
| EBMUD | 5.6 | 71.0 | 60.3 | 1.4 |
| FSSD | 13.9 | 65.5 | 24.8 | 1.4 |
| *CCSD* | *44.1* | *42.2* | *5.5* | *1.4* |

Desulfinyl was not detected at detection limit of 0.3 μg/kg dry weight

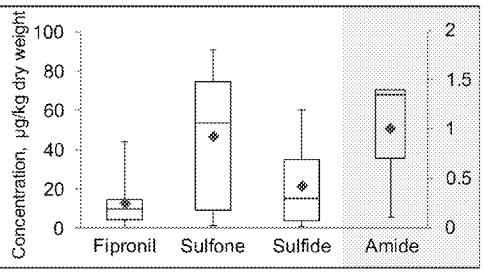


Figure 4. Concentrations of fipronil and its degradates detected in sludge samples obtained from 8 wastewater treatment plants in northern California in 2015. Highlighted in red italics are facilities not performing anaerobic treatment. In the plot, amide concentrations (highlighted blue) correspond to the secondary *y*-axis. See Table 1 for definition of site abbreviations.

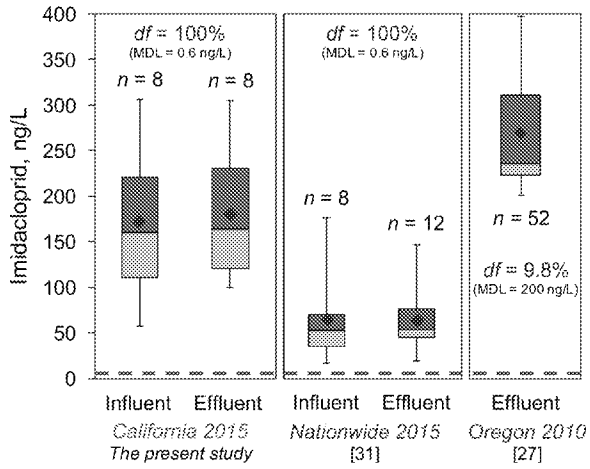


Figure 5. Detected concentrations of imidacloprid (ng/L) in 8 wastewater treatment plants in northern California and summary of data from previous studies [27,31]. Dashed blue horizontal line indicates European Union freshwater predicted no-effect concentration value [17]. df = detection frequency; MDL = method detection limit.

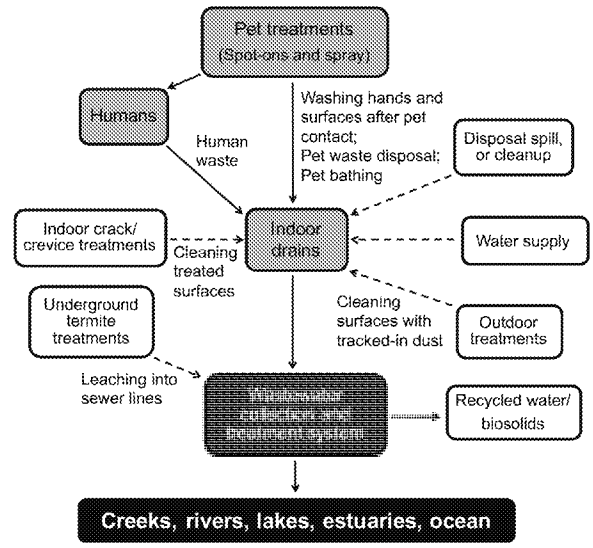


Figure 6. Conceptual model for sources of fipronil and imidacloprid in municipal wastewater. Dashed lines denote pathways believed to be relatively small in the present study. Uses without a clear pathway (e.g., containerized baits) and with unlikely pathways (e.g., air transport and deposition) [50] are excluded from the figure.

effluents with detectable imidacloprid had levels in the range of 202 ng/L to 387 ng/L (Figure 5) [27]. A limit of quantification of 200 ng/L [27], significantly higher than the method detection limit of the present study (0.6 ng/L), may account to some extent for the difference in results observed. Higher overall concentrations and detection frequencies in effluent from northern California may reflect regional, seasonal, and/or climate-related differences from other sampled facilities, such as lower dilution caused by drought-related water use reductions, presence of pests during all seasons because of the mild coastal climate, and pesticide use responding to regional pest pressures (e.g., high flea populations in California coastal areas) [30], suggesting the value of understanding regional and seasonal factors to inform estimates of the potential loading of imidacloprid in wastewater.

*Fipronil and imidacloprid sources*

Examination of the per capita influent load of wastewater pollutants can be instructive, as it eliminates effects of flow differences among WWTPs and provides a reference discharge quantity for comparison with various potential sources. For the 7 typical municipal WWTPs in the study, the measured per capita influent loads expressed in nanomoles per person per day, for fiproles ($54 \pm 9$ nmol/person/d, mean $\pm$ standard deviation) and imidacloprid ($190 \pm 80$ nmol/person/d) were relatively consistent. The concentration of contaminants in wastewater influent can vary by several orders of magnitude over the course of a single day for a single analyte, so a low variability in daily per capita load suggests a larger number of ubiquitous sources rather than episodic concentrated sources [33–35]. Although episodic discharges from spills, cleanup, or improper disposal of a pesticide are possible, such an event was not likely captured during this sampling event, as evidenced by similar per capita influent loads at all WWTPs.

As regulated pesticides, fipronil and imidacloprid have limited indoor uses in California: pet flea control, crack and crevice treatments intended for out of the way locations, and containerized bait stations [1,9]. All uses are considered unlikely to entail discharges to the sewer system [10,11].

A simple conceptual model (Figure 6) clarifies potential pathways between fipronil and imidacloprid use and the sewer system and facilitates examination of the potential importance of each discharge source. Although no fipronil and imidacloprid products, for either indoor or outdoor use, are designed to be directly discharged to indoor (sewer) drains, actions after use—such as bathing pets treated with flea control products, washing hands and other surfaces that come in contact with treated areas or pets, or wet-mopping treated indoor areas—provide indirect pathways for introduction of both pesticides to the sewer. Outdoor-use pesticides can enter sewer systems through cleaning of surfaces containing pesticides tracked indoors by pets and humans after outdoor applications. Leaching into sewer lines (which are not water tight) during underground building treatments is another possible pathway. However, leaking sewer laterals as a pathway would vary as a function of age of building sewer infrastructure. Drinking water supply may potentially be a source for contaminants. Although imidacloprid and fipronil concentrations have not been reported in any of the diverse water systems serving the 7 WWTPs, there is no or very limited agricultural and urban influence on drinking water sources for all but 2 of the WWTPs (Supplemental Data, Table S8). The low variability of per capita influent loads in the 7 municipal WWTPs, despite differing building sewer infrastructure ages and differing water sources, renders tap water an unlikely or minor source that nevertheless deserves future investigation. A third indirect source—human waste—has been verified for imidacloprid, which is known to be present in human urine [36], but is only suspected for fipronil based on rat oral exposure studies where most fiprole mass was excreted in feces [37]. As noted, episodic discharges from spills, cleanup, and improper disposal are likely small pathways, given the low data variability.

An examination of potential pathways suggests that pet flea treatments may be the primary source of both pesticides in WWTP influent. Pet flea treatments have typical concentrations of 9.8% fipronil and 9.1% imidacloprid; single pet applications involve 0.07 g to 0.4 g fipronil or 0.04 to 0.4 g imidacloprid. In contrast, the only other type of uncontainerized indoor treatments—crack and crevice applications—entails pesticide concentrations of 0.05% or less. Even the highest concentration (0.05%), professional-sized (33-g) fipronil crack and crevice

product on the market contains <0.02 g fipronil; 40 to 1200 of these crack and crevice products would need to be emptied directly into the sewer daily to achieve the influent fipronil load at the 7 typical municipal WWTPs sampled (see the Supplemental Data for calculations).

The transport of pesticides indoors from outdoor applications has been well documented [38], and fipronil is nearly omnipresent in indoor residential dust [39]. Reported concentrations were >20 times higher in households owning a dog treated with fipronil-containing spot-on products than those without treated pets [39], suggesting that residues associated with flea treatments for pets are more significant than residues tracked indoors from outdoor applications.

Dog and cat ownership in the United States is 0.24 and 0.27 per capita, respectively [40,41], and survey data indicate that 75% of dog and cat households use a flea/tick product [42]. The prevalent use of flea and tick treatment is consistent with ubiquitous rather than episodic source. Residues associated with pet products may be transferred to companions or indoor spaces [43] or may be transported directly down the drain through bathing. Washing surfaces and materials that have come in contact with and accumulated pesticides, such as companion hands, pet bedding, and companion clothing, represents indirect pathways of pesticides to wastewater.

A 2012 study [43] that quantified the mass of fipronil transferred to cotton gloves worn while owners petted their dogs for 2 min reported levels of 5600 μg 24 h postapplication, declining to 220 μg at 2 wk, and 76 μg at 4 wk, which coincides with recommended retreatment. To evaluate flea and tick treatments as a potential indirect source to wastewater, the daily influent loads measured at the WWTP are converted to mass per dog per day. Assuming fipronil has a 30% market share, each fipronil-treated dog would provide 300 μg/d, suggesting (by comparison with the hand transfer quantities) that hand washing and other indirect transfer could be a large source (see the Supplemental Data for calculations). Because flea treatments remain on pet fur for weeks after treatment [43], dog washing may result in an even greater proportion of applied pesticide discharging to the sewer system. Although comparable studies are not available for imidacloprid, the similarity of use patterns suggests comparable pathways. Imidacloprid's higher solubility may result in a larger portion washing off during bathing.

The results for the San Francisco airport WWTP, which has no on-site residential or animal populations, were the lowest reported influent concentrations for both analytes, with a midrange effluent concentration for imidacloprid compared with the other WWTPs evaluated. Airport facilities managers report no professional applicator use of imidacloprid, and fipronil is only applied via containerized baits and gels. This suggests that indirect pathways from off-site use are the major source, but does not eliminate the potential for discharges associated with nonprofessional use of retail products. Transport of pesticides through hand washing, introduction of human waste of the airport's transient population, and discharges associated with retail product use could contribute the relatively small influent loads (fiproles, 79 μmol/d; imidacloprid, 400 μmol/d) received at this unique WWTP. Available retail products contain similar mass as the total daily load (fiproles, 38 μmol/container; imidacloprid, 878 μmol/container).

*Environmental implications*

Several studies have demonstrated that organic micropollutants (such as pharmaceuticals, personal care products, and household pesticides) and their degradates persist through conventional wastewater treatment [32,44–46]. Wastewater effluents flow continuously into diverse freshwater and saltwater aquatic environments, creating continuous ecosystem exposure to entrained pollutants. The potential for pesticides in wastewater effluents to cause adverse effects on aquatic species depends not only on their concentrations, but also on site-specific factors at the discharge point such as dilution (if any), presence of substances that may alter bioavailability or toxicity (e.g., dissolved organic carbon), and presence of other toxicants with cumulative toxic effects. Water available to dilute effluents may already contain both fipronil-related compounds and imidacloprid from upstream sources [20]. Partitioning and fate in the receiving water can have long-term implications not revealed solely by effluent pesticide concentrations, a possibility for fipronil and its degradates, which are likely to partition into sediment based on log $K_{OW}$ values > 4 (Supplemental Data, Table S2).

A direct comparison of fiprole and imidacloprid concentrations in these effluents with established chronic toxicity reference values [15,17] suggests a potential for harm to aquatic species, meriting further investigation. Prior work has shown that for the majority of freshwater macroinvertebrates, fipronil degradates are more toxic than fipronil [15]; these findings were not available when the USEPA established its aquatic life benchmarks in 2007 [16]. A comparison of detected concentrations with 96-h EC50 values for *Chironomus dilutus* is shown in Figure 1. It can be seen that degradate (fipronil sulfone, sulfide, and amide) concentrations in effluent were increased relative to influent as a result of the treatment. Therefore, change in fiprole distribution did not result in a marked decrease in toxicity and potentially may have increased toxicity for 7 of the 8 WWTPs (see Supplemental Data, Table S9, for calculation). A similar conclusion was reached in a prior study on a WWTP discharging into a freshwater environment [25]. However, these toxicity thresholds are derived from data for freshwater organisms in laboratory conditions, and thus may not accurately reflect potential risks in an estuarine environment such as San Francisco Bay. The present study did not include measurement of the toxicity or bioavailability of the effluent-borne insecticides to downstream biota. At present, there is a lack of toxicity data on susceptible receptor organisms in these saltwater settings. As a result, appropriately protective thresholds such as PNECs have not been established for saltwater environments, and thus further investigation is called for.

Other factors specific to San Francisco Bay may inform an evaluation of the potential impacts of effluent discharges containing these pesticides, particularly as findings from the present study suggest that existing treatment technology appears to be unable to significantly remove these pesticides. For example, effluents discharged in the southernmost regions of the Bay experience less dilution and oceanic exchange than effluents discharged in more central locations. Effluents are not the only pathway for these pesticides to enter San Francisco Bay; other studies have detected fipronil and imidacloprid in the region's urban creeks and storm water discharges [6,15,19,47]. As predicted, fipronil and its degradates have partitioned to Bay sediment (data publicly available via cd3.sfei.org), with levels of fipronil sulfone approaching a toxicity threshold for freshwater invertebrates [48]. As a result, the parent compound has been classified as an emerging contaminant of moderate concern for San Francisco Bay [49]. Imidacloprid has not yet been evaluated by local authorities relative to the region's tiered risk and management action framework for emerging

contaminants [49]. Results from the present study may inform ongoing regional monitoring and management efforts as well as broader state and federal actions to limit the potential for environmental contamination with these pesticides and to develop modeling approaches to better predict pesticide wastewater discharge and fate in municipal WWTPs and in receiving waters.

These findings must be considered in light of other important considerations. A one-time sampling event, as conducted in the present study and other similar studies [25,29,31,45], cannot assess the effects of temporal variations in pesticide use and discharge, particularly as it relates to seasonality. Although the San Francisco Bay region is less likely to display large shifts in urban flea control pesticide use, with its mild climate and relatively uniform flea pest pressures [30], seasonality is likely to be a major influence in other urban areas with marked seasonal temperature shifts. Another consideration is the potential for pesticide contamination of the water sources supplying tap water to urban residents. Although most of the source waters for San Francisco Bay urban water supplies related to the present study are essentially free of agricultural, urban, and treated wastewater influences (Supplemental Data, Table S8), the same cannot be said for the water supplies of many other regions. Source or tap water testing for relevant pesticides is likely to be an important element of studies conducted elsewhere. A third consideration concerns the wastewater treatment technology used. Although the treatment trains employed by WWTPs participating in the present study were diverse, they do not cover all available technologies. Alternate technologies, such as reverse osmosis, may have different impacts on pesticide levels, and could be explored in future studies.

## CONCLUSIONS

The levels of fiproles and imidacloprid measured in wastewater influent and treated wastewater effluent suggest that conventional treatment has little promise for reducing the release of fiproles or imidacloprid into the environment once discharged to the sewer system. An investigation of potential sources suggests that pet flea and tick products are the primary source of fiprole and imidacloprid to WWTP influent. Additional work is needed to quantify the relative contribution of suggested sources and pathways (e.g., pet products, human waste, underground termite treatments). The findings of the present study, particularly identification of pet products as a likely primary source, can inform upcoming USEPA risk assessments for fipronil and imidacloprid, which for the first time will evaluate the aquatic risks associated with urban use of these pesticides [10,11]. Available toxicity thresholds have been established only for freshwater environments, highlighting the need for saltwater toxicity studies to evaluate the risks of these pesticides to the ecological health of estuarine and ocean environments in addition to freshwater systems.

*Supplemental Data*—The Supplemental Data are available on the Wiley Online Library at DOI: 10.1002/etc.3673.

*Acknowledgment*—The present study was funded by the Regional Monitoring Program for Water Quality in San Francisco Bay (Contribution 783) and in part by Award Numbers R01ES015445 and R01ES020889, and their supplements from the National Institute of Environmental Health Sciences (NIEHS). The authors acknowledge participants from the following wastewater treatment plants in our study: Palo Alto Regional Water Quality Control Plant, Fairfield Suisun Sewer District, Central Contra Costa Sanitary District, East Bay Municipal Utility District, East Bay Dischargers Authority, City of San Mateo Wastewater Treatment Plant, San Jose/Santa Clara Regional Wastewater Facility, and San Francisco International Airport Sanitary Waste Treatment Plant. The authors also thank E.F. Willis-Norton for assistance with the earlier 2014 sampling campaign and P.L. Tenbrook for assistance with development of the conceptual model. Reviews by D. Muir, W. Arnold, H. Stapleton, wastewater participants, and anonymous reviewers led to significant improvements.

*Disclaimer*—The views expressed herein are those of the authors and do not necessarily reflect those of the California Department of Pesticide Regulation, the NIEHS, or the National Institutes of Health.

*Data Availability*—Most of the data are available in the Supplemental Data. Additional data requests should be directed to the corresponding author (halden@asu.edu).

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# Supporting Information

## Passage of Fiproles and Imidacloprid from Urban Pest Control Uses Through Wastewater Treatment Plants in Northern California

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**Summary**

This supporting information contains 10 pages, including 9 tables and 1 figure.



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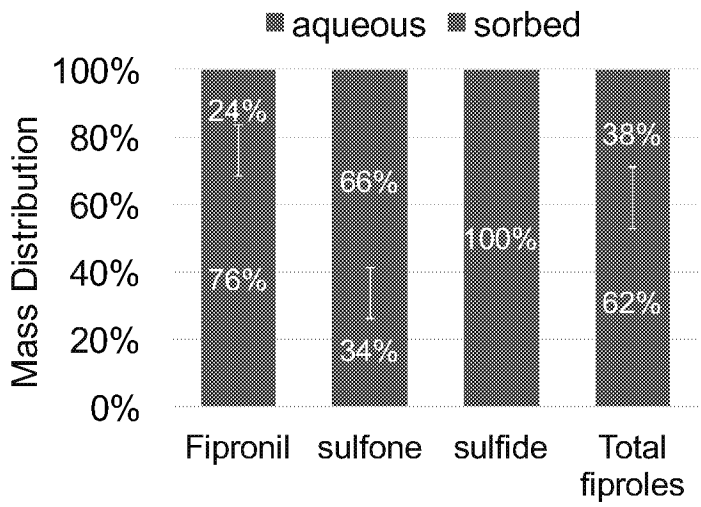


**Figure S1.** Relative distribution of the mass of imidacloprid, fipronil and major degradates between the dissolved and sorbed state (suspended solids) of wastewater influent samples ($n$=8). Error bars represent standard deviation among 8 samples.

**Data Statistics**

A paired two tailed $t$-test was performed ($\alpha = 0.05$) to compare influent and effluent concentration. Differences were determined at the $p < 0.05$ significance level. Shapiro-Wilk test was performed to assess the normality of the data.

For comparison of all fipronil related compounds in aqueous phase influent and effluent at all eight WWTPs, $p$ value for Shapiro-Wilk test was 0.17, and $p$ value for a paired two tailed $t$-test was 0.95.

For comparison of imidacloprid concentration in influent and effluent at seven WWTPs, $p$ value for Shapiro-Wilk test was 0.18, and $p$ value for a paired two tailed $t$-test was 0.49.

**Instrument Selection for the Analysis of Fipronil and Its Degradates**

Fipronil and degradates – sulfone, sulfide and amide showed higher sensitivity on LC-MS/MS, and desulfinyl on GC-MS/MS. Considering isotope dilution method was used, matrix effects were not a considerable concern. Therefore, analytes were analyzed with separate instruments to achieve the best result.



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**Table S1.** Mass Spectrometric Parameters for the Detection of Analytes and Isotope-Labeled Surrogate Standards

| analyte | $Q_1$ (m/z) | $Q_3$ (m/z) | $Q_3'$(m/z) | DP (V) | CE(V) | EP (V) | CXP (V) |
|---|---|---|---|---|---|---|---|
| imidacloprid | 256 | 175.1 | 209.2 | 50 | 30 | 10 | 8 |
| fipronil | 434.9 | 329.9 | 250.0 | -70 | -10 | -24 | -5 |
| -sulfone | 450.8 | 281.8 | 414.7 | -70 | -10 | -40 | -4 |
| -sulfide | 418.7 | 382.8 | 262.1 | -75 | -10 | -18 | -5 |
| -amide | 386.7 | 350.8 | 281.9 | -70 | -10 | -40 | -9 |
| -desulfinyl | 384.9 | 305.8 | 254.7 | -110 | -6 | -28 | -15 |
| internal standards | | | | | | | |
| imidacloprid-$d_4$ | 260.1 | 213.1 | 179.2 | 76 | 25 | 6 | 14 |
| fipronil ($^{13}C_2{}^{15}N_2$) | 438.8 | 333.8 | 254 | -65 | -10 | -24 | -13 |
| -sulfone ($^{13}C_4{}^{15}N_2$) | 456.8 | 420.5 | 287.6 | -75 | -10 | -24 | -15 |

**Table S2.** Method detection limit in different matrices and Octanol-Water Partition Coefficient ($K_{OW}$)

| analyte | MDL | | Log $K_{ow}$ |
|---|---|---|---|
| | wastewater | solids | |
| | ng/L | ng/g | |
| Imidacloprid | 0.6 | 1.1 | - 0.41 |
| Fipronil | 0.1 | 0.1 | 4.00 |
| sulfide | 0.2 | 0.1 | 4.42 |
| sulfone | 0.1 | 0.1 | 4.82 |
| amide | 0.3 | 0.1 | 5.43 |
| desulfinyl | 0.8 | 0.2 | 4.22 |



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**Table S3.** Total detected concentrations of fipronil and its degradates in influent and effluent samples obtained from 8 wastewater treatment plants in northern California in 2015 (ng/L).

| WWTP | Fipronil | | sulfone | | sulfide | | amide | | desulfinyl | |
|---|---|---|---|---|---|---|---|---|---|---|
| | inf | eff | inf | eff | inf | eff | inf | eff | inf | eff |
| SFTP | 13.3 | 14.3 | 4.1 | 1.1 | 2.5 | 1.3 | <0.3 | 0.6 | <0.8 | <0.8 |
| PARP | 59.2 | 31.2 | 21.1 | 10.4 | 1.5 | 1.7 | <0.3 | 2.5 | <0.8 | <0.8 |
| SJSC | 54.5 | 42.9 | 26.6 | 16.3 | 2.0 | 1.8 | <0.3 | 1.1 | <0.8 | <0.8 |
| SLWP | 45.3 | 36.6 | 24.0 | 12.3 | 0.8 | 1.6 | <0.3 | 1.4 | <0.8 | <0.8 |
| SMWP | 82.2 | 48.3 | 31.2 | 12.7 | 3.4 | 2.5 | <0.3 | 0.7 | <0.8 | <0.8 |
| EBMUD | 61.7 | 44.3 | 22.1 | 7.6 | 2.1 | 1.5 | <0.3 | <0.3 | <0.8 | <0.8 |
| FSSD | 49.6 | 34.4 | 16.7 | 11.4 | 0.9 | 1.9 | <0.3 | 4.1 | <0.8 | <0.8 |
| CCSD | 88.1 | 48.6 | 28.2 | 9.8 | 5.2 | 2.0 | <0.3 | 2.4 | 1.0 | 1.2 |

**Table S4.** Aqueous and sorbed phase concentration of fipronil and its degradates in influent samples obtained from 8 wastewater treatment plants in northern California in 2015.

| WWTP | Fipronil | | sulfone | | sulfide | |
|---|---|---|---|---|---|---|
| | aqueous phase, ng/L | sorbed phase, ng/g | aqueous phase, ng/L | sorbed phase, ng/g | aqueous phase, ng/L | sorbed phase, ng/g |
| SFTP | 8.6 | 4.7 | 1.1 | 3.0 | < 0.2 | 2.5 |
| PARP | 47.0 | 37.9 | 7.8 | 41.4 | < 0.2 | 4.5 |
| SJSC | 42.1 | 41.6 | 7.3 | 58.2 | < 0.2 | 6.3 |
| SLWP | 30.9 | 27.9 | 7.9 | 31.3 | < 0.2 | 1.6 |
| SMWP | 60.9 | 51.7 | 10.3 | 50.7 | < 0.2 | 8.3 |
| EBMUD | 45.5 | 47.6 | 5.4 | 49.1 | < 0.2 | 6.1 |
| FSSD | 42.7 | 28.9 | 7.7 | 38.3 | < 0.2 | 3.6 |
| CCSD | 74.9 | 42.3 | 11.9 | 52.2 | < 0.2 | 16.6 |



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**Table S5.** Molar distribution of fipronil and its degradates in treatment streams of 8 WWTPs in northern California in 2015.

| | influent - particulates | | | | |
|---|---|---|---|---|---|
| WWTP | Fipronil | sulfone | sulfide | amide | desulfinyl |
| SFTP | 46% | 28% | 26% | 0% | 0% |
| PARP | 46% | 48% | 6% | 0% | 0% |
| SJSC | 40% | 54% | 6% | 0% | 0% |
| SLWP | 47% | 51% | 3% | 0% | 0% |
| SMWP | 47% | 45% | 8% | 0% | 0% |
| EBMUD | 47% | 47% | 6% | 0% | 0% |
| FSSD | 42% | 53% | 5% | 0% | 0% |
| CCSD | 38% | 46% | 16% | 0% | 0% |
| | | | | | |
| | influent - dissolved phase | | | | |
| WWTP | Fipronil | sulfone | sulfide | amide | desulfinyl |
| SFTP | 89% | 11% | 0% | 0% | 0% |
| PARP | 86% | 14% | 0% | 0% | 0% |
| SJSC | 86% | 14% | 0% | 0% | 0% |
| SLWP | 80% | 20% | 0% | 0% | 0% |
| SMWP | 86% | 14% | 0% | 0% | 0% |
| EBMUD | 90% | 10% | 0% | 0% | 0% |
| FSSD | 85% | 15% | 0% | 0% | 0% |
| CCSD | 86% | 13% | 0% | 0% | 1% |
| | | | | | |
| | influent - total | | | | |
| WWTP | Fipronil | sulfone | sulfide | amide | desulfinyl |
| SFTP | 67% | 20% | 13% | 0% | 0% |
| PARP | 73% | 25% | 2% | 0% | 0% |
| SJSC | 67% | 30% | 3% | 0% | 0% |
| SLWP | 65% | 33% | 1% | 0% | 0% |
| SMWP | 71% | 26% | 3% | 0% | 0% |
| EBMUD | 72% | 25% | 3% | 0% | 0% |
| FSSD | 74% | 24% | 1% | 0% | 0% |
| CCSD | 73% | 23% | 4% | 0% | 1% |
| | | | | | |
| | effluent - total | | | | |
| WWTP | Fipronil | sulfone | sulfide | amide | desulfinyl |
| SFTP | 83% | 6% | 8% | 3% | 0% |
| PARP | 69% | 22% | 4% | 5% | 0% |
| SJSC | 70% | 25% | 3% | 2% | 0% |
| SLWP | 71% | 23% | 3% | 3% | 0% |
| SMWP | 76% | 19% | 4% | 1% | 0% |
| EBMUD | 83% | 14% | 3% | 0% | 0% |
| FSSD | 67% | 21% | 4% | 8% | 0% |
| CCSD | 76% | 15% | 3% | 4% | 2% |
| | | | | | |



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| | sludge | | | | |
|---|---|---|---|---|---|
| WWTP | Fipronil | sulfone | sulfide | amide | desulfinyl |
| SFTP | 5% | 42% | 50% | 3% | 0% |
| PARP | 55% | 42% | 3% | 0% | 0% |
| SJSC | 4% | 62% | 32% | 3% | 0% |
| SLWP | 7% | 65% | 27% | 1% | 0% |
| SMWP | 12% | 58% | 29% | 1% | 0% |
| EBMUD | 4% | 50% | 45% | 1% | 0% |
| FSSD | 13% | 61% | 25% | 1% | 0% |
| CCSD | 48% | 44% | 6% | 1% | 0% |

**Sample Collection and Analysis, 2014**

Influent and effluent fipronil samples were 24-hr composites collected by the respective WWTP in fall 2014. Composites were transferred to 1 L amber glass containers. Neither disinfectant nor preservative (Kathon CG/ICP) was added to the samples. Samples were refrigerated below 4$^{o}$ C and shipped overnight to the California Department of Fish and Wildlife's Water Pollution Control Laboratory (WPCL; Rancho Cordova, CA, USA) within 7 days of collection.

The WWTP influent and effluent samples were analyzed for fipronil, fipronil desulfinyl, fipronil sulfide, fipronil sulfone, fipronil amide, and fipronil desulfinyl amide using WPCL Method LC-007. A 500 mL aliquot was pre-filtered using Whatman #5 filter paper, 2.5 µm particle retention. The aliquot was then passed then through a pre-conditioned solid phase extraction cartridge (6 cc Waters Oasis HLB cartridge). The sample was eluted with methanol and 0.1% formic acid, evaporated under nitrogen, and brought up to a final volume of 2 mL with methanol. The extract was then filtered into a vial using a 13mm syringe filter with 0.45 µm PTFE membrane. The analysis was performed on an Agilent 1200 series LC system with a G6410A QQQ Mass Spectrometer with electrospray ionization in negative polarity. A Phenomenex, Kinetex XB-C18, 2.1 x 100 mm, 2.6 µm column was used.

This method has limitations compared to that used for samples collected in 2015 and discussed in the main text, including the lack of isotopically labeled standards. Recoveries determined on matrix spikes were within 35% of expected values, with the exception of fipronil desulfinyl amide (56%). Recoveries determined on blank spikes were within 20% of expected



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values. However, field replicates, especially for influent, varied as much as two-fold, suggesting these measurements are semi-quantitative. The method detection limit (MDL) was 0.5 ng/L for all analytes. Two of the six analytes, fipronil amide and fipronil desulfinyl amide, were not detected in samples from all eight WWTPs.

**Table S6.** Detected concentrations (ng/L) of fipronil and its degradates in influent and effluent samples obtained from 8 wastewater treatment plants in northern California in 2014. Fipronil amide and fipronil desulfinyl amide were not detected above the method detection limit (0.05 ng/L). See *Sample Collection and Analysis, 2014*, below, for further information.

| | Fipronil | | sulfone | | sulfide | | desulfinyl | |
|---|---|---|---|---|---|---|---|---|
| WWTP | inf | eff | inf | eff | inf | eff | inf | eff |
| SFTP | 10 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 | <0.5 |
| PARP | 70 | 50 | 8 | 3 | <0.5 | <0.5 | <0.5 | <0.5 |
| SJSC | 125 | 107 | 8 | 5 | 2 | 1 | <0.5 | <0.5 |
| SLWP | 111 | 50 | 8 | 10 | <0.5 | 3 | <0.5 | <0.5 |
| SMWP | 45 | 98 | 5 | 9 | 1.9 | 3 | <0.5 | 1.7 |
| EBMUD | 56 | 75 | 12 | 6 | 3.5 | <0.5 | 5.5 | 2 |
| FSSD | 71 | 40 | 12 | 7 | 2 | 2 | <0.5 | 8 |
| CCSD | 146 | 93 | 16 | 11 | 3 | 3 | 3 | 14 |

**Table S7.** Detected concentrations of imidacloprid in influent and effluent samples obtained from 8 wastewater treatment plants in northern California in 2015.

| WWTP | Imidacloprid, ng/L | |
|---|---|---|
| | influent | effluent |
| SFTP | 58.1 | 177.6 |
| PARP | 109.4 | 100.1 |
| SJSC | 206.9 | 264.9 |
| SLWP | 261.4 | 219.9 |
| SMWP | 171.8 | 150.8 |
| EBMUD | 306.1 | 305.2 |
| FSSD | 110.5 | 83.8 |
| CCSD | 149.5 | 127.4 |



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**Table S8.** WWTP service area drinking water suppliers and their water supply characteristics.

| WWTP | WWTP Service Area Drinking Water Supplier(s) | Are there agricultural, urban runoff or wastewater influences on water supply? |
|---|---|---|
| SFTP | San Francisco Public Utilities Commission (SFPUC) | No.<br>SFTP and SMWP receive water from a pipeline coming from the Hetch Hetchy Reservoir and Alameda County watersheds. The SFPUC water supply is free of wastewater discharges and virtually unaffected by urban or agricultural runoff.[1] |
| SMWP | SFPUC | |
| SLWP | East Bay Municipal Utilities District (EBMUD) | Very Limited.<br>Typically supplied almost entirely by sources with little or no urban or agricultural use in the watershed. However, during summer 2015, a limited amount of water was sourced from the Sacramento River at Freeport,[2] which is influenced by upstream agricultural and urban runoff as well as wastewater discharges.[3] USGS monitored the Sacramento River twice monthly for two years near the intake and only detected fipronil and imidacloprid during a single large winter storm event, with RLs of 4.9 ng/L (imidacloprid) and 2.9 ng/L (fipronil), 1.8 (fipronil sulfide), 3.5 (fipronil sulfone), 1.6 ng/L (desulfinyl fipronil).[4] |
| EBMUD | EBMUD | |
| PARP | SFPUC (≈75%), Santa Clara Valley Water District (SCVWD) (<20%); local groundwater (<10%) | Very Limited.<br>Non-SFPUC water supplies may show limited influence of agricultural and urban runoff and wastewater. |
| SJSC | SFPUC, SCVWD, local groundwater, San Jose Water Company reservoir | Very Limited.<br>Non-SFPUC water supplies may show limited influence of agricultural and urban runoff and wastewater. |
| FSSD | Solano Water Project (Lake Berryessa), State Water Project/North Bay Aqueduct; local groundwater (limited use) | Yes.<br>Lake Berryessa has very limited urban or agricultural activity in its watershed. The State Water Project / North Bay Aqueduct water supply is the San Joaquin / Sacramento River Delta, which is influenced by upstream agricultural and urban runoff and wastewater discharges.[5] |
| CCSD | EBMUD (>50%), Contra Costa Water District (CCWD) | Yes.<br>The CCWD water supply is the San Joaquin/Sacramento River Delta, which is influenced |



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| | | |
|---|---|---|
| | | by upstream agricultural and urban runoff and wastewater discharges.[5] |

[1] San Francisco Public Utilities Commission (SFPUC) 2008. *San Francisco Water Quality Protection Plan.*
[2] EBMUD Water Operations Department (2015). Water Supply Briefing. May.
[3] Starr Consulting (2015). Sacramento River Watershed Sanitary Survey 2015 Update Report. December.
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[5] CALFED Bay-Delta Program (2005). Delta Region Drinking Water Quality Management Plan. June.

**Table S9.** *Chironomus dilutus* - hazard quotient (HQ) of the influent and effluent aqueous wastewater streams. HQ calculation does not consider degradates amide and desulfinyl.

$$HQ_{Stream} = \frac{C_{fipronil}}{33} + \frac{C_{sulfone}}{8} + \frac{C_{sulfide}}{10}$$

| WWTP | $HQ_{effluent}$ / $HQ_{influent}$ |
|---|---|
| SFTP | 1.8 |
| PARP | 1.0 |
| SJSC | 1.6 |
| SLWP | 1.5 |
| SMWP | 1.1 |
| EBMUD | 1.2 |
| FSSD | 1.2 |
| CCSD | 0.8 |

**Kathon CG/ICP**

In this study 600 mg/L of Kathon CG/ICP (purchased from Sigma-Aldrich Corp., St. Louis, MO, USA) preservative was added to wastewater to disinfect the samples. During method development, potential for interference of Kathon CG/ICP with detection was tested in deionized water, synthetic wastewater (made of peat moss) and wastewater. Results showed that Kathon CG/ICP did not interfere with the LC-MS/MS and GC-MS/MS measurement of insecticides.



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## Comparison of Gel Product Fipronil Content to Influent Load

The highest concentration (0.05%) fipronil crack and crevice gel products was identified from the California Department of Pesticide Regulation database of registered pesticide products [1]. This product is packaged in "professional-sized" 33 g applicator units that, at 0.05% fipronil by weight, each contain 0.0165 g fipronil. At the seven community-serving WWTPs, daily influent fipronil loads measured were 0.7 g (SLWP) to 19.9 g (SJSC) fipronil, the equivalent of the fipronil content of 40 to 1,200 tubes of this gel product.

## Estimated Influent Load per Fipronil-Treated Dog

Per capita dog ownership was estimated to be 0.24 dog / person on the basis of the July 1 2015 US population of 321 million [2] and total US dog ownership of 77.8 million [3]. An estimated 75% of pet owners use flea/tick treatment products [4]. Fipronil's market share among these products was roughly estimated at 30% based on product registration data [1], a retail shelf survey [5] and interviews of northern California dog owners. On this basis, an estimated 22% of all dogs receive fipronil treatments, which translates to 0.055 fipronil-treated dogs / person. The median daily per capita fipronil influent load (17 µg/person*day) divided by 0.055 fipronil-treated dogs / person generates an estimated daily fipronil load for per fipronil-treated dog of 300 µg.

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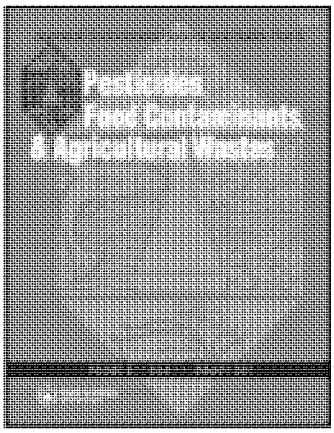


**Journal of Environmental Science and Health, Part B: Pesticides, Food Contaminants, and Agricultural Wastes**
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lesb20

# Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments

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Published online: 31 Aug 2012.

**To cite this article**: Melinda Bigelow Dyk , Yu Liu , Zhenshan Chen , Helen Vega & Robert I. Krieger (2012) Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments, Journal of Environmental Science and Health, Part B: Pesticides, Food Contaminants, and Agricultural Wastes, 47:10, 913-924, DOI: 10.1080/03601234.2012.706548

**To link to this article**: http://dx.doi.org/10.1080/03601234.2012.706548

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*Journal of Environmental Science and Health, Part B* (2012) **47**, 913–924
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ISSN: 0360-1234 (Print); 1532-4109 (Online)
DOI: 10.1080/03601234.2012.706548

# Fate and distribution of fipronil on companion animals and in their indoor residences following spot-on flea treatments

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Use of fipronil {5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile CAS 120068–37-3} topical pet products on dogs and cats introduces low level residues into residences. Distribution and fate studies of fipronil on pets and in residences were performed to evaluate potential determinants of human exposure. Fipronil, desulfinyl fipronil, fipronil sulfone and fipronil sulfide were measured on hair clippings and brushed hair. The derivatives usually represented <10% of fipronil applied. Cotton gloves worn over impervious nitrile gloves, cotton cloths placed indoors in locations frequented by pets, and cotton socks worn by residents as direct dosimeters collected fipronil and its derivatives listed above in low amounts during 4-week study periods. Subsequent acid hydrolysis urine biomonitoring did not reveal significant excretion of biomarkers at ppb levels. The human exposure potential of fipronil is low relative to levels of health concern.

**Keywords:** Fipronil, companion animals, flea control, biomonitoring, exposure assessment.

## Introduction

Prevention, control and/or eradication of fleas and other pests of companion animals using pesticides introduce residues at some level into their residences. Pets treated with insecticide may represent a subchronic, low-level, and moving point-source of pesticide exposure due to extensive pet contact and pesticide residue transfer via direct contact, dust, and dander to the residence itself. Chronic exposure may occur due to the residential and environmental persistence of fipronil including exposures resulting from more extensive use of spot-on products by veterinarians.[1] Surface residue will be of greatest significance with direct skin contact or hand-to-mouth transfer and ingestion resulting from contact with the pet. Pesticides applied as collars, dips, shampoos, spot-on treatments and oral medications are extensively used to control fleas and other pests of companion animals.[1]

Fipronil (CAS 120068–37-3) is a broad-spectrum phenylpyrazole insecticide and acaricide discovered by Rhône-Poulenc in 1987 and first registered for use by the United States Environmental Protection Agency (USEPA) in 1996. Registered fipronil uses include products for golf course and turf management, seed treatments, structural pest control, and crop protection in addition to topical pet care products. Post-marketing surveillance revealed a risk of mild, temporary neurological (50%), ocular (44%), gastrointestinal (28%), respiratory (27%), and dermal (21%) symptoms/signs among 103 cases reporting adverse effects at 11 U.S. healthcare facilities, 2001–2007.[2] The insecticidal action of fipronil results from disruption of the insect central nervous system via the gamma-aminobutyric acid (GABA) regulated chloride channel following either contact or ingestion. It blocks the GABA-gated chloride channels of neurons in the central nervous systems, resulting in neural excitation and death.[3]

Previous environmental studies have documented the fate and distribution of fipronil in agricultural settings. The formation of desulfinyl fipronil by photolysis, fipronil sulfone produced by aerobic metabolism in soils, fipronil sulfide formed anaerobically in soils and water, and desulfinyl fipronil amide formed aerobically in soils and by hydrolysis at basic pH represent the production of lipophilic derivatives and putative animal and human metabolites.[4–6] The desulfinyl and sulfone derivatives of fipronil are more persistent and less selective between arthropods and mammals than the parent insecticide.[7,8] The extent of formation of fipronil derivatives on companion animals is unknown. A previous study using cotton glove dosimeters to periodically wipe the peltage of treated dogs indicated that fipronil

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Received April 16, 2012.

is present and transferable to gloves for up to four weeks after application of a spot-on product.[9]

Fipronil was found on 40% of floor wipes of hard surfaces primarily in the kitchen area of a stratified, nationally representative sample of 1131 residences in a 2005–2006 USEPA study.[10] The mean and geometric mean were 0.16 ng/cm$^2$ and 0.002 ng/cm$^2$, respectively. In addition to use as a spot-on insecticide for flea treatment and control, fipronil baits are used indoors against ants and cockroaches and as a termiticide in structural pest control. The occurrence of fipronil residues indoors was also reported by Mahler[11] who observed higher levels of total fipronil (fipronil + desulfinyl fipronil + fipronil sulfide) in indoor dust than in outdoor dust collected in Austin, TX. The median fipronil level represented 86% of the 33.1 $\mu$g total fipronil/kg dust in the 23-sample study. The molar proportion of the total fipronil residues composed of fipronil sulfide was greater indoors than outdoors, and the proportion composed of desulfinyl fipronil was greater outdoors than indoors. The concentrations of fipronil were normally distributed with the exception of five outliers representing residences with a dog. Dust and dander of dogs likely contributed to the distribution and persistence of total fipronil residues in those Texas residences, but the significance of indoor surface residues with respect to human exposure is unknown.

Products containing fipronil are important flea and tick treatments.[1] Fipronil and its derivatives may persist on the peltage of companion animals and transfer to residences and humans by direct contact.[2] Therefore, pet owner exposure to these chemicals at some level is inevitable. Since some fipronil products are registered for crop protection resulting in food residues, aggregate exposures and risk characterization are required in accord with the Food Quality Protection Act (FQPA) of 1996. Published data are lacking concerning the indoor fate and distribution of spot-on fipronil flea control products, although the pesticide use in crop protection requires an aggregate risk assessment consistent with the FQPA. These studies concern the fate and distribution of fipronil on companion animals and in their environments and the results may be important to planning and conduct of future aggregate exposure assessments.

Pets were recognized as a potential source of 2,4-D track-in, which initiated the search for other pesticides applied outside being brought indoors.[12] Subsequently, pet track-in of diazinon as a potential exposure source was measured in a pilot study.[13] Morgan et al.[13] investigated the potential for dogs to transfer diazinon from outdoor turf treatments to the indoor environment using fur clippings, fur wipes, paw measurements and surface residues. Higher residues were recorded on residents than on a dog, and the authors suggested the dog represented a good vehicle for transport of pesticide from outdoors to the indoor environment. In a larger scale study, Morgan et al.[14] included t-shirts, gloves, dosimeter wipes and urine biomonitoring. The investigators observed that occupants and their dog transferred diazinon residues from treated outdoor turf into the home. However, the dog was observed as the highest source of transfer. Biomarker levels from urine collection were not significantly higher than pre-application levels despite the introduction of diazinon into the home.

During the same era (2000–2003) biomonitoring of adults and their children following use of chlorpyrifos shampoos or flea collars recorded urine 3, 5, 6-trichloro-2-pyridinol (TCPy) levels.[15] Biomarkers represented exposures well below levels expected to be associated with adverse effects or even depressed levels of cholinesterases, an alternate biomarker of chlorpyrifos exposure in pet product studies.[15,16] In general, persons who had contact with pets treated with chlorpyrifos flea protection products had small increases in the excretion of TCPy. These pilot studies were opportunistic (or situational exposure monitoring) and involved small numbers of participants who used products according to label instructions. The results demonstrated very limited human exposure following use of this class of flea control products.[15,17]

Other studies have concerned pet owner exposure from companion animals treated with specific pet care products. Boone et al.[18] used 100% cotton gloves as a dosimeter to collect transferable residues from dogs after they were treated with flea dip containing chlorpyrifos. Briefly, investigators wearing cotton gloves petted dogs for 5 min. The gloves were extracted to measure transferable residue. This study showed chlorpyrifos residues were transferred for up to 21 days after flea dip use. After Boone et al.,[18] additional studies have been published using gloves as a dosimeter of pet product transfer.[9, 19–23] These studies demonstrate the persistence of available residue on pet hair, but data have not been validated for the estimation of potential human exposure.

The present studies were intended to measure the fate and distribution of fipronil and its primary lipophilic derivatives (Fig. 1) on companion animals and in residences following spot-on fipronil treatments for fleas. Here we report the results of observational studies following spot-on treatments of dogs and cats in the residences of 12 California families. These studies were done using Frontline® products that were supplied to the participants who in turn used the spot-on treatments with only label guidance (Table 1). As such, they satisfy our definition of situational exposure monitoring. Sampling of pet hair of companion animals and indoor surfaces was performed by pet owners in addition to urine biomonitoring for putative fipronil biomarkers.

## Materials and methods

### *Study protocols*

The study protocol was approved by the University of California, Riverside, Institutional Review Board and the California Department of Pesticide Regulation,

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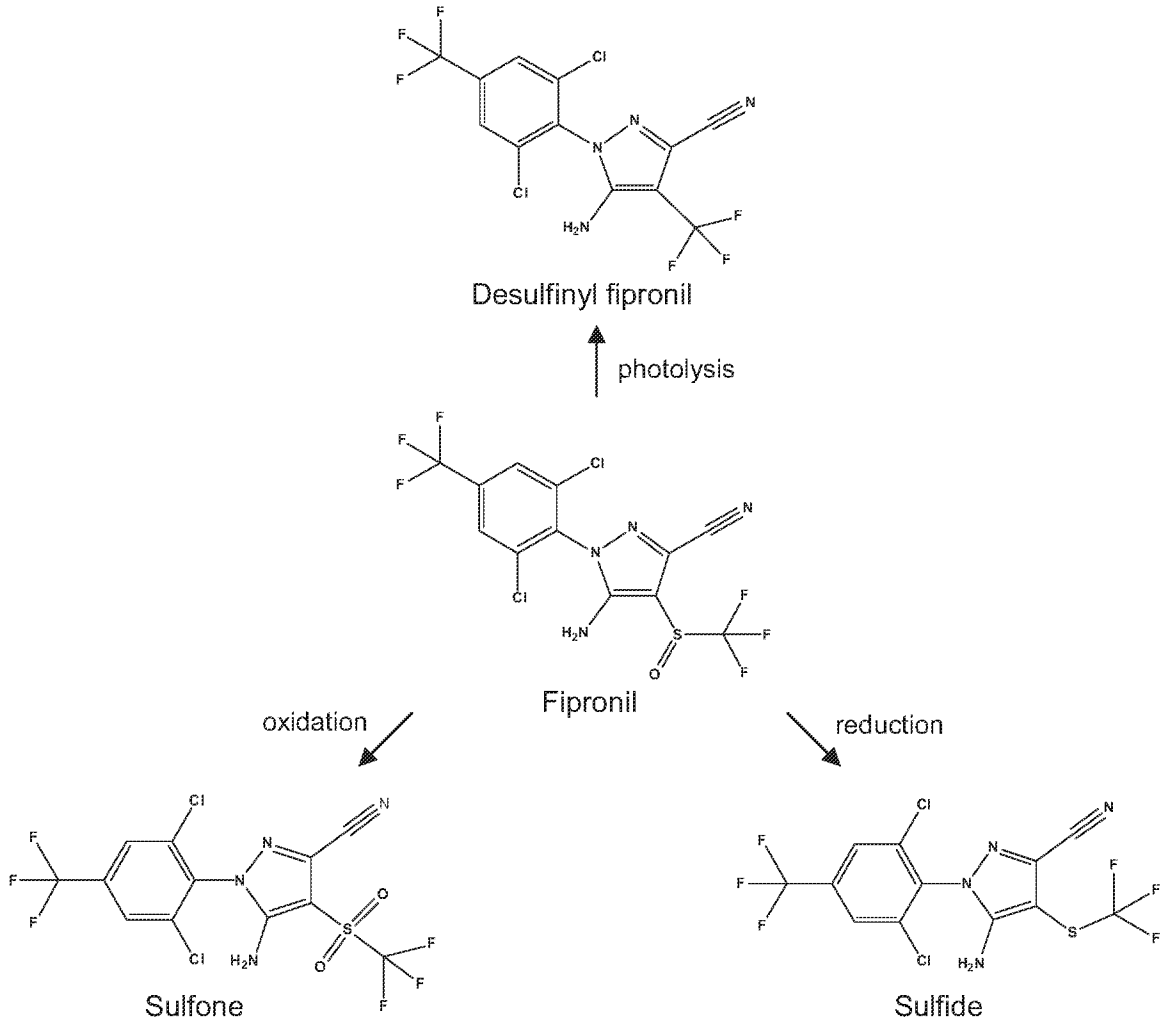


**Fig. 1.** Fipronil and its lipophilic derivatives routinely measured on companion animals and in their indoor residences.[4, 6]

Sacramento, CA. This protocol addressed all aspects of participant recruiting and residential sampling in addition to urine biomonitoring. A separate Animal Use Protocol was also obtained from the University of California, Riverside, Institutional Animal Care and Use Committee. All participants completed a general health questionnaire that was confidentially evaluated by a physician's assistant and each gave written consent to participate in these observational studies.

### *Frontline® fluorescence*

A solution of 1% Tinopal® CBS-X was prepared in the commercial Frontline® Plus formulations (Table 2) that

**Table 1.** Frontline® application schedule from label information.

| *Companion animal size* | *Weight of dog (kg)* | *Product size (mL)* | *Conc. (g/mL)* | *Fipronil (g) in product used* | *Maximum dosage (mg/cm$^2$)*[a] |
|---|---|---|---|---|---|
| Very small dog | 2–10 | 0.67 | 0.1 | 0.067 | 0.039 |
| Small dog | 10–20 | 1.34 | 0.1 | 0.134 | 0.027 |
| Medium dog | 20–40 | 2.68 | 0.1 | 0.268 | 0.035 |
| Large dog | 40–60 | 4.02 | 0.1 | 0.402 | 0.033 |
| Cat | ≥1 | 0.5 | 0.1 | 0.050 | 0.046 |

[a]Maximum dosage = mg active substance/body surface area of animal. Surface area of companion animals was calculated using (12.3 * Body Weight (g) $^{0.65}$; Wildlife Exposure Factors Handbook, EPA/600/R-93/187 http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2799.

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**Table 2.** Fipronil and derivatives measured in Frontline® products.

| *Frontline®* | | *Amount measured in product (mg)* | | | *Percent measured in product* | | |
|---|---|---|---|---|---|---|---|
| *Lot #* | *Type* | *Fipronil* | *Fipronil sulfone* | *Fipronil sulfide* | *Fipronil* | *Fipronil sulfone* | *Fipronil sulfide* |
| B12001 | Cat | 46 | 1.8 | 5 | 9.2 | 0.48 | 1.1 |
| B46102 | Med dog | 66 | 2.4 | 7.3 | 9.9 | 0.35 | 1.1 |
| B40409 | XL dog | 136 | 3.4 | 11 | 10 | 0.26 | 0.8 |
| – | Mean ± SD | – | – | – | 9.8 ± 0.52 | 0.36 ± 0.11 | 1.0 ± 0.16 |

Three lots of Frontline® were analyzed using GCMS to determine the amount of fipronil and derivatives in the product. Derivatives were measured according to their characteristic ions. Fipronil–367; Fipronil sulfone–383; Fipronil Sulfide; 353. Concentrations were calculated using a linear regression of a 5-point standard curve (0.01 to 15 ppm).

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were used following label instructions. Preliminary studies using a handheld black light showed that the excipient and tracer moved together on the dogs' skin (not shown). Pre-application, application, and 5 h and 24 h post-application photographs were taken using a Nikon D60 camera fitted with a 18–55mm f/3.5–5.6G AF-S DX VR Nikon Zoom Lens. Six UVA black lights (19" fluorescent; 60 W/120 volt) and one 6" mini-fluorescent white light illuminated a custom-built photo studio.[24]

### *Transferable pet residues (TPR)*

Cotton gloves were worn by participants while petting their companion animals for 2 min to establish TPR. Pet owners wore 100% cotton gloves (Fisherbrand® lightweight 100%, 300 $cm^2$) over nitrile gloves (High Five Brand Purple) that were impervious to fipronil as demonstrated in separate preliminary studies not reported here. Participants were instructed to wipe the full torso of their dogs or cats, but a specific protocol was not utilized. TPR samples were collected pre-application and 24 h, 1, 2, 3, and 4 weeks post-application. Cotton gloves were stored in pre-labeled polyethylene freezer bags and kept by participants in home freezers until transport to the laboratory and final storage at about −10°C until analysis.

Gloves were extracted twice with 150 mL ethyl acetate:acetone (9:1) by shaking at high frequency for 30 min using an Eberbach shaker. The extract was concentrated to ~10 mL using a Büchi rotovap and centrifuged for 5 min at 4774 $g_{max}$ (Sigma 4–10; 5000 rpm; Rotor# 11140). The centrifuged extracts were concentrated to ~5 mL under nitrogen. Extracts were initially analyzed using high pressure liquid chromatography, but all reported results were obtained using GCMS. Fipronil, fipronil sulfone, desulfinyl fipronil, and fipronil sulfide were determined by weight in the final ethyl acetate extract (Fig. 1). Recoveries of fipronil from spiked glove samples (n = 15) ranged 90% to 95% (Table 3).

### *Total hair residues (THR, μg/g)*

THR was measured on hair collected on a de-shedding tool (Bamboo® Fur Buster™, Target®, Moreno Valley,

**Table 3.** Fipronil and derivatives transferred to cotton gloves from dogs and cats.

| | | *μg/Pair gloves* | | | |
|---|---|---|---|---|---|
| *Animals* | *Sampling interval* | *Fipronil* | *Desulfinyl fipronil* | *Fipronil sulfone* | *Fipronil sulfide* |
| Dogs (n = 11) | Pre-application | 97 (nd–380) | 1.8 (nd–3.2) | 3.1 (nd–4.6) | 2.1 (nd–6.6) |
| | 24 h | 5600 (380–17000) | 110 (nd–413) | 440 (1.6–2300) | 66 (6.6–220) |
| | 1 week | 530 (47–1800) | 45 (nd–303) | 49 (1.7–300) | 13 (0.65–43) |
| | 2 weeks | 220 (52–800) | 31 (nd–158) | 45 (2.1–210) | 0.74 (0.74–11) |
| | 3 weeks | 120 (21–560) | 24 (nd–102) | 34 (0.62–120) | 4.1 (0.27–28) |
| | 4 weeks | 76 (5–240) | 10 (nd–61) | 15 (0.81–35) | 2.3 (nd–6.7) |
| Cats (n = 14) | Pre-application | 0.75 (nd–0.94) | 0.5 (nd–0.5) | 0.24 (nd–0.48) | Nd |
| | 24 h | 880 (94–2800) | 3.3 (nd–21) | 26 (nd–64) | 24 (nd–130) |
| | 1 week | 160 (8.2–340) | 1.3 (nd–7.8) | 10 (0.046–34) | 6.0 (0.19–17) |
| | 2 weeks | 53 (3.8–300) | 0.71 (nd–1.9) | 4.4 (0.77–13) | 1.3 (nd–5.3) |
| | 3 weeks | 30 (1.4–190) | 0.50 (nd–1.6) | 2.8 (nd–8.1) | 0.63 (nd–3.3) |
| | 4 weeks | 17 (0.23–110) | 0.36 (nd–1.2) | 1.8 (nd–5.8) | 0.43 (nd–2) |

Levels of fipronil and derivatives transferred from dogs and cats to cotton gloves worn over nitrile gloves by participants while petting their companion animals for 2 min. Fipronil and derivatives were extracted and analyzed using GCMS. [a]nd are non-detectable levels of liquid spikes representing LOQs of 0.005 to 0.16 μg/pair gloves.

**Table 4.** Fipronil and derivatives on hair samples brushed from dogs and cats.

| | | *μg/g Hair* | | | |
|---|---|---|---|---|---|
| *Participant* | *Sampling interval* | *Fipronil* | *Desulfinyl fipronil* | *Fipronil sulfone* | *Fipronil sulfide* |
| Dogs (n = 9) | Pre-application | 110 (nd–300) | 1.1 (nd–1.2) | 13 (nd–13.2) | 1.9 (nd–3.4) |
| | 24 h | 2100 (52–6100) | 8.8 (nd–18) | 120 (2.1–340) | 14 (1.7–42) |
| | 1 week | 400 (32–770) | 17 (nd–83) | 73 (1.0–380) | 8.8 (0.50–14) |
| | 2 weeks | 200 (7.8–540) | 4.9 (nd–21) | 43 (0.23–110) | 2.9 (nd–10) |
| | 3 weeks | 74 (0.58–400) | 2.7 (nd–8.7) | 24 (nd–46) | 2.0 (nd–8.0) |
| | 4 weeks | 39 (0.19–250) | 1.6 (nd–3.6) | 17 (nd–57) | 1.3 (nd–5.2) |
| Cats (n = 12) | Pre-application | 3.0 (nd–10) | 1.6 (nd–1.7) | 1.1 (nd–1.2) | 0.76 (nd–0.81) |
| | 24 h | 670 (55–2700) | 4.2 (nd–20) | 54 (1.0–230) | 32 (1.4–100) |
| | 1 week | 160 (10–600) | 1.4 (nd–7.5) | 4.6 (nd–18) | 3.5 (0.15–7.5) |
| | 2 weeks | 42 (4.7–200) | 0.41 (nd–1.3) | 1.6 (nd–3.8) | 1.1 (nd–4.1) |
| | 3 weeks | 21 (2.7–68) | 0.26 (nd–0.59) | 1.8 (nd–4.8) | 2.2 (nd–3.1) |
| | 4 weeks | 15 (2.2–67) | 0.18 (nd–53) | 2.1 (nd–6.0) | 0.80 (nd–3.1) |

Mean levels of fipronil and derivatives on hair from dogs and cats collected by pet owners who brushed their companion animals for 2 min using a Bamboo® Fur Buster™de-shedding tool. Fipronil and derivatives were extracted and analyzed using GCMS.
Mean calculated from measurable fipronil levels not including non-detects which are represented in the range (low–high) μg fipronil/g hair. [a]nd are non-detectable levels of liquid spikes representing LOQs of 0.012 to 0.85 μg/g hair.

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CA) following a 2 min brushing of the full torso (likely including the application site) of the companion animals. THR samples were collected pre-application and 24 h, 1, 2, 3, and 4 weeks post-application. Hair samples were stored in pre-labeled polyethylene freezer bags and kept in home freezers until transport to the laboratory and final storage at about −10°C until analysis. Hair samples were analyzed as above and results reported as μg/g hair (Table 4). Recoveries of fipronil from spiked hair samples (n = 15) ranged 9%1to 97%.

### *Hair clippings*

Pet owners collected hair clippings using electric shears. Hair from about 3.8 $cm^2$ zones on the neck, mid-back, top of tail/lumbar zone, and right side and left sides of the animals were obtained pre-application and at 5 h, 24 h and 1, 2, 3, and 4 weeks post-application. Hair samples were stored in polyethylene bags in a freezer until transport to the laboratory where they were kept frozen (−10°C) until preparation for analysis.

Hair clippings were weighed and extracted twice in 50 mL ethyl acetate:acetone (9:1) by shaking at high frequency for 30 min using an Eberbach shaker. Extracts were passed through an acetone pre-rinsed coffee filter into a round bottom flask and concentrated to ~10 mL using a Büchi rotovap. The extracts were filtered using a Fisherbrand® G8 glass fiber filter and a Fisherbrand 13 mm 0.45 μM syringe filter. Volume was reduced to ~5mL under nitrogen before analysis. Recoveries of liquid spikes from hair samples (n = 15) ranged 9%1to 97% (Table 5).

### *Pet space dosimeters (PSD)*

PSDs were used to measure residues transferred to cotton cloths placed by pet owners in areas frequented by their

**Table 5.** Fipronil on hair clippings from dogs following Frontline® applications.

| *Dog* | *Sampling interval* | *Neck* | *Mid- back* | *Top of tail* | *Right side* | *Left side* |
|---|---|---|---|---|---|---|
| Hair Clipping (n = 4) | Pre-application | 21 (nd–21) | 8 (nd–8) | 7 (nd–7) | nd | Nd |
| | 5 h | 144 (22–300) | 68 (15–200) | 41 (7–120) | 110 (nd–110) | 40 (nd–63) |
| | 24 h | 93 (16–230) | 104 (31–180) | 44 (10–130) | 24 (8–64) | 30 (11–77) |
| | 1 week | 37 (18–78) | 76 (27–130) | 14 (11–22) | 25 (10–62) | 17 (8–18) |
| | 2 weeks | 69 (10–130) | 44 (23–60) | 15 (7–20) | 10 (5–19) | 12 (nd–15) |
| | 3 weeks | 52 (18–100) | 23 (6–36) | 22 (nd–40) | 83 (nd–230) | 19 (nd–23) |
| | 4 weeks | 82 (34–15) | 37 (nd–74) | 32 (20–55) | 101 (nd–105) | 19 (7–35) |

Levels of fipronil on clipped hair samples at five sites collected by pet owners who clipped hair. Fipronil and derivatives were extracted and analyzed using HPLC. Mean calculated from measurable fipronil levels not including non-detects which are represented in the range (low to high) μg fipronil/g hair from about 3.8 $cm^2$ skin area.
[a] nd are non-detectable levels of liquid spikes representing LOQs of 0.062 to 1.4 μg/g hair.

**Table 6.** Mean fipronil and derivatives on pet space dosimeters of companion animals.

| | | *Mean ($\mu g/cm^2$)(SD)* | | | |
|---|---|---|---|---|---|
| *Animals* | *N* | *Fipronil* | *Desulfinyl fipronil* | *Fipronil sulfone* | *Fipronil sulfide* |
| Dogs | 11 | 1.0 (3.0) | 0.0047 (0.011) | 0.16 (0.42) | 0.0057 (0.010) |
| Cats | 27 | 0.15 (0.55) | 0.00016 (0.00026) | 0.0050 (0.0092) | 0.00088 (0.0017) |

Cotton textiles (1380 $cm^2$) were used as potential Pet Space Dosimeters (PSDs) to measure transferability of fipronil and derivatives from dogs and cats to indoor areas frequented by treated pets. PSDs were usually in place for the first 14 days (1–2 weeks) after Frontline® application. Fipronil and derivatives were extracted and analyzed using GCMS. Mean and standard deviation calculated from measurable fipronil levels not including non-detects.
Non-detectable levels of liquid spikes on the cotton cloths represented LOQs $3.6 \times 10^{-5}$ to $1.1 \times 10^{-4}$ $\mu g/cm^2$.

dogs or cats (beds, furniture, play areas, and cat trees). The PSDs were machine washed twice using laundry detergent, machine rinsed three times with water, and machine dried prior to use. PSDs were placed in two homes for consecutive 2-week periods following fipronil applications to measure the time-dependent transfer of fipronil and its derivatives.

After each sampling period, the PSDs were stored in a freezer (−10°C) in polyethylene freezer bags until analysis. Briefly, the dosimeters were cut into 1 inch squares, extracted twice with 350 mL ethyl acetate:acetone (9:1) in a 1000 mL Nalgene® HDPE wide mouth bottle, shaken at high frequency for 30 min using an Eberbach shaker. Extracts were concentrated to ~10 mL using a Büchi rotovap and centrifuged for 5 min at 4774 $g_{max}$. Extracts were concentrated to ~5 mL under nitrogen followed by GCMS analysis. Fipronil and the desulfinyl, sulfone, sulfide, and destrifluoromethyl sulfinyl fipronil were determined by weight in ethyl acetate extracts. Recoveries of liquid spikes of the analytes on PSDs (n = 15) ranged 80% to 85% (Table 6).

### *Transferable indoor residue (TIR)*

TIR is an indicator of the amount of fipronil transferred to persons from their indoor environment. TIR represents the residues recovered from cotton socks worn for 2 h nightly for 7 consecutive days during a 4-week post-application period. After each use, cotton socks were placed into a polyethylene freezer bag in a home refrigerator during each 7-day period. Clean socks were supplied after 7 days and the samples were stored in a freezer (−10°C) until analysis. Some participants who had previously used fipronil products collected pre-application samples for two days prior to the reapplication. Three participants also collected TIRs for two consecutive months to investigate potential indoor accumulation when fipronil was used monthly.

TIR samples were cut to facilitate sample handling (~1 inch squares) and extracted using 300 mL ethyl acetate:acetone (9:1) in a soxhlet apparatus refluxed for 3 h. All extracts were concentrated to ~10 mL using a Büchi rotovap, centrifuged, and analyzed using GCMS. Recoveries of spiked samples (n = 15) ranged 95% to 99% (Table 7).

### *Urine biomonitoring*

Participants collected either first morning voids or 24 h complete urine specimens for putative biomarker analysis. A complete set of urine specimens consisted of 2 pre-application and 12 to 15 post-application specimens. Seven sets of morning voids and five sets of 24 h specimens were available. The urine specimens were stored frozen (−20°C) prior to analysis. Solids were removed by centrifugation prior to acid hydrolysis of 100 mL aliquots following addition of 10 mL 6N HCl and heating at 60°C for 1 h. The

**Table 7.** Fipronil and derivatives transferred to cotton socks from indoor environment.

| | | *$\mu g$/Pair-h socks* | | | |
|---|---|---|---|---|---|
| *Application* | *Samplinginterval* | *Fipronil* | *Desulfinyl fipronil* | *Fipronil sulfone* | *Fipronil sulfide* |
| Residences with dogs and cats (n = 12) | Pre-application | 3.4 (nd–3.4) | 1.7 (nd–1.7) | 7.4 (nd–7.4) | 0.25 (nd–0.25) |
| | 1 week | 47 (2.5–220) | 1.1 (nd–2.0) | 2.7 (0.41–7.4) | 0.58 (nd–2.1) |
| | 2 weeks | 11 (0.54–36) | 0.68 (nd–1.5) | 2.0 (0.08–16) | 0.22 (nd–0.69) |
| | 3 weeks | 4.1 (0.36–16) | 0.29 (nd–0.53) | 1.2 (nd–8.1) | 0.15 (nd–0.41) |
| | 4 weeks | 2.7 (0.29–8.9) | 0.28 (nd–0.53) | 0.95 (0.07–6.4) | 0.16 (nd–0.27) |

Transferable Indoor Residues were measured on cotton socks worn by participants after Frontline® application to companion animals. Cotton socks were worn for ~2 h per night for a week (about 14 h total). New socks supplied weekly. Fipronil and derivatives determined following soxhlet extraction and GCMS analysis. Fipronil and derivatives were extracted and analyzed using GCMS. Non-detectable levels of liquid spikes represented LOQs of 0.005 to 0.03 $\mu g$/pair socks-h.

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hydrolysates were cooled and adjusted with 6N KOH to pH 6 to 8. Fipronil SPE extraction was adapted from Ngim and Crosby.[25] The SPE cartridges were conditioned with 5 mL volumes of ethyl acetate, methanol, and water prior to loading the hydrolysates or standards in hydrolyzed urine. Samples were poured into reservoirs and allowed to pass through the cartridge at 1–2 mL/min. The cartridges were dried for a minimum of 3 h under vacuum. Samples were eluted with 10 mL ethyl acetate (1 mL/min) into 15 mL centrifuge tubes. Eluates were prepared for analysis by concentrating to dryness under nitrogen and dissolving in 250 $\mu$L ethyl acetate. The standard hydrolyzed urine contained fipronil and four putative metabolites including fipronil sulfone, fipronil sulfide, desulfinyl fipronil and destrifluoromethyl sulfinyl fipronil.

## Analysis

Fipronil and selected derivatives were analyzed using a HP 6890 gas chromatograph with a HP MSD 5973 in electron impact ionization (EI) mode at ionization energy of 70 eV. The MS transfer line temperature was 280°C. Injector temperature was 250°C. Injection (1 $\mu$L) was done in the splitless mode at a pressure of 45 psi. Helium was used as carrier gas with constant flow of 1.0 mL/min. Chromatographic separation was performed on a HP-5ms capillary column (30 m × 0.32 mm i.d. × 0.25 $\mu$m film; Agilent Technologies, Inc. USA). The initial column temperature of 50°C was increased at 15°C/min to 270°C and held constant for 28.5 min. For quantification the GC-MS was operated in a selective ion monitoring (SIM) mode: 388 desulfinyl fipronil, 353 fipronil sulfide, 367 fipronil, 320 destrifluoromethyl sulfinyl fipronil, and 383 fipronil sulfone. The instrumental limit of detection was 0.01–0.03 ppm.

Summary tables include mean ± s.d. values that represent measurable levels not including "non-detects" which are only represented in the range of the levels of fipronil or its derivatives recorded for any sample type.

## Results and discussion

### *Application of Frontline® and fipronil dosage on companion animals*

Fipronil in a proprietary emollient was dispensed from an easy-to-open plastic applicator in 5 volumes based upon animal weight (Table 1). As a result the product for "very small dogs" contained 0.67 mL and that for "large dogs" (40–60 kg) contained 4.02 mL product. Treatment as directed resulted in application of a similar dosage (0.039 to 0.033 mg/cm$^2$) based upon the estimated surface area of the respective dogs (Table 1). The recommended dosage for cats (≥1 kg) was of the same order (0.046 mg/cm$^2$).

The chemical composition of 3 lots of Frontline® was determined using GCMS analysis of residual product remaining in applicators after spot-on treatment of a cat and 2 dogs (Table 2). Each lot contained fipronil (9.8% ± 0.52% w/w) and lesser amounts of fipronil sulfone (0.36% ± 0.11%) and fipronil sulfide (1.0% ± 0.16%). The content of the active ingredient was consistent with the product labels. Other fipronil derivatives detected in these studies resulted from environmental or biological transformations. The measures of those derivatives in applied Frontline® were not considered in subsequent analyses of the distribution of fipronil.

### *Visualization of the distribution of Frontline® on dogs*

The rapid, time-dependent movement of the emollient containing fipronil was easily observed with the aid of the fluorescent indicator and UVA illumination in a custom pet studio that afforded control of light (Fig. 2). At the time of application, the spot-on product covered a circular area of about 5 cm diameter that expanded rapidly by 5 h after the application to about 6 cm × 10 cm. Less intensive fluorescence was also visible on the sides and toward the tail of the treated dogs. Hair clippings confirmed the presence of fipronil on the neck, middle back and at the base of the tail after 5 h. After 24 h the more intense fluorescent zone was about 9 cm × 20 cm with greatest intensity at the neck (230 $\mu$g fipronil/g hair) and mid-back (150 $\mu$g/g). After 48 h only the application site could be visualized although hair clippings contained measurable residues documenting the persistence of the flea product (Table 5).

During the days immediately following application of spot-on products, light "oiling" of the peltage of the cats and dogs is often visible. At this time direct contact with skin may result in transfer of product (Fig. 3) as shown in the photo of study staff after handling a dog during the fluorescent tracer studies. Subsequent residue measurements of pet hair and indoor surfaces have shown fipronil and its

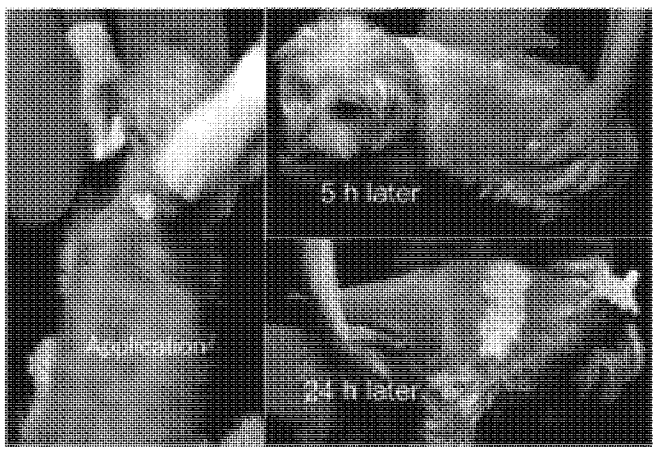


**Fig. 2.** Application and distribution of fipronil was demonstrated at 5h and 24h using Frontline® containing 1% Tinopal® CBS-X and UVA black lights photographed in a darkened photo studio (color figure available online).

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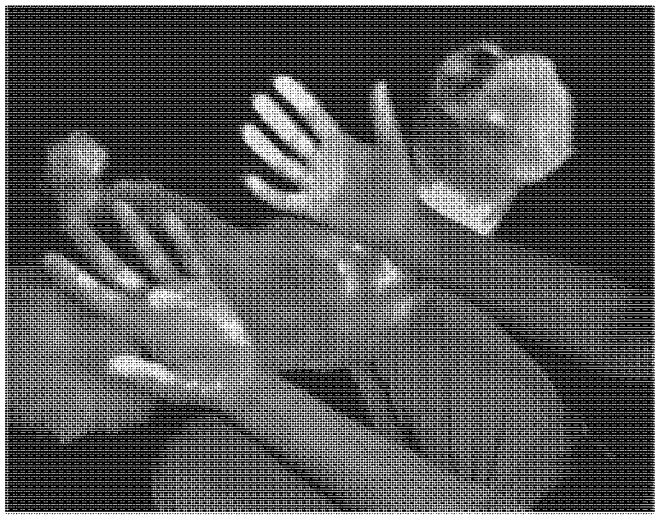

**Fig. 3.** Handling of a dog treated with Frontline® containing 1% Tinopal® CBS-X fluorescent tracer revealed contamination of hands during routine application and handling of a treated dog (color figure available online).

lipophilic derivatives to be persistent and dispersed in indoor environments where spot-on products have been used for flea control.

### *Hair clippings from dogs following spot-on treatment*

Direct evidence of the time-dependent distribution of fipronil was obtained from analysis of the hair clippings from the neck, middle back, top of tail/lumbar zone, right side and left sides of the dogs (Table 5). The clippings (about 3.8 $cm^2$) were well tolerated, but were inconvenient for both investigators and the companion animals due to additional animal handling required for sampling. Serial sampling was also difficult due to the limited area available which prohibited actual sample replication. Within 5 h of Frontline® application, fipronil was detected at each of the sampling sites. The levels of fipronil on the back and neck were higher than those at the base of the tail and on the sides of the 4 dogs used in this aspect of these studies. The results in Table 5 reveal the considerable variability of the means and the high and low values of the fipronil levels ($\mu$g/g) of the hair clipping samples during the 4-week study period.

### *Transferable hair residues (THR) brushed from dogs and cats*

Brushed hair samples from dogs and cats were a more convenient means to sample hair than clippings for evaluation of the fate and persistence of fipronil and its derivatives. Higher levels of fipronil were present on hair brushings from dogs than cats (Table 4). On dogs, fipronil THR ranged 0.19–6100 $\mu$g/g hair with a mean of 2000 $\pm$ 1900 $\mu$g/g hair (Table 4). On cats, fipronil THR ranged 2.2–2700 $\mu$g/g hair with a mean of 700 $\pm$ 840 $\mu$g/g hair (Table 4). Dog hair had significantly higher fipronil levels than cat hair (t-test; p-value = 0.04). Fipronil THR levels declined to the greatest extent between 24 h and 1 w in the hair brushings of both dogs and cats. Fipronil sulfone was the most prominent derivative present in each sample and lesser amounts of desulfinyl fipronil and fipronil sulfide were also present (Fig. 1; Table 4).

The results in Table 4 also reveal the considerable variability of the means and the range of high and low values of fipronil and the three derivatives ($\mu$g/g) in the hair brushings through the 4-week study period. It is important to note that the effectiveness of fipronil as a flea product depends upon levels in the sebum on the skin. As a result the hair clipping and brushing measurements represent the fate and persistence of fipronil on the pet per se, but hair samples must be considered an indirect indicator of the exposure potential of the insecticide toward fleas.

### *Residential pet space dosimeters (PSDs)*

During the first week following application of fipronil the peltage levels (THR and hair clippings) declined more dramatically than during the subsequent weeks of the study period (Table 5). PSDs were placed in the residence to gauge the extent of loss of residue to areas frequented by pets. The cotton cloths were generally well-tolerated or even used as toys, but some pets disturbed the cloths and avoided significant contact with the PSDs. In every case, fipronil was the predominant residue on the cloths (Table 6). Although the ever-present fipronil derivatives were also measured, the levels on the cotton cloths were relatively lower than those found on brushed hair (Table 4) or cotton gloves (Table 3).

### *Fipronil and derivatives transferred to cotton gloves from dogs and cats*

Cotton gloves have become a useful tool for assessment of the fate and distribution of pet products on companion animals.[1] Gloves have been used to assess potential hand exposure[26, 27]). After Boone et al.,[18] additional research with well-known spot-on treatments (Frontline®, Revolution®, and Advantage®) using gloves as dosimeters has demonstrated long term, low-level, potential pesticide residue transfer.[1] The relationship of transferred residues to absorbed dose has not been established in any published study and glove residues have not been validated to reconstruct human pet product exposure.[1]

The percent fipronil transferred to cotton gloves following Frontline® applications ranged from 0.56% to 11% of the applied dose on dogs and 0.50% to 6.5% on cats. Fipronil transferred to gloves used on dogs ranged from a high of 17,000 at 24 h to 5 $\mu$g/pair after 4 weeks (overall mean 5100 $\pm$ 5800 $\mu$g/pair; Table 3). Amounts transferred from cats ranged from 2,800 to 0.23 $\mu$g/pair (overall mean 930 $\pm$ 900 $\mu$g/pair; Table 3) during the same interval. The

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difference between the cat and dog transferable residues was not significant ($P$-value = 0.104). In both cases the residues declined most dramatically during the first week following the spot-on treatments, and, thereafter, the glove residues declined exponentially with a half-life of about 1 week.

Three fipronil derivatives (desulfinyl, sulfone, and sulfide) were measured in the 24 h glove samples in greater amounts than were present in Frontline® (Table 2). The derivatives were also measured on gloves (Table 3) in similar levels as occurred in hair brushings (Table 4). There was considerable animal-to-animal variability. Desulfinyl fipronil was observed as transferable residue (0.36–410 $\mu$g/pair gloves) from all dogs except one (Tables 3). Fipronil sulfone (0.28–2300 $\mu$g/pair gloves) and sulfide (0.062–220 $\mu$g/pair gloves) were measured on all glove samples.

On cats, desulfinyl fipronil was detected on at least one pair of gloves during the treatment cycle from all cats (both those that resided primarily indoors or primarily outdoors). The occurrence and amounts of fipronil (0.0082–21 $\mu$g/pair gloves) were low and varied. Fipronil sulfone (0.046–71 $\mu$g/pair gloves) and fipronil sulfide (0.052–130 $\mu$g/pair gloves) were also present on the majority of the glove samples collected during each study period. The amounts of derivatives were lower on gloves with lesser amounts of fipronil (i.e., 3 and 4 week samples).

### *Transferable indoor residue measured using cotton sock dosimeters*

Fipronil, fipronil desulfinyl, fipronil sulfone, and fipronil sulfide were measured as TIR on cotton socks (Table 7) likely representing widespread dispersal of the residues in dust and dander within residences. Fipronil residues declined with time on all TIR samples. Lesser amounts of the derivatives accumulated on the dosimeters as the fipronil residues declined during the study period (Table 7). Limited pre-application sampling of homes in which fipronil products had previously been used up to 9 months earlier revealed low level fipronil residues on socks (results not shown). During the 4-week study periods, the highest levels of fipronil and its derivatives were collected during the first week following the spot-on application. The amount of fipronil transferred to cotton socks during the 4-week study periods was about 0.5% (n = 12) of the amount applied to the companion animals in homes with predominantly vinyl, nylon carpet, and/or hardwood floor coverings.

Cotton sock dosimeters may be a means to estimate potential personal chemical exposure. Socks represent a point of direct human contact with transferable surface residues during routine indoor activities and the results may be amenable to potential exposure assessment for adults and children. The residue levels on socks as well as those of other measures employed in these studies demonstrate decreasing exposure potential with time.

Cotton socks are an alternative dosimeter to gloves. Socks have been used to estimate dermal exposure to chemicals.[28–31] Cotton sock dosimeters can estimate dermal transfer, pesticide exposure, and transferable indoor residue to residents.[30–33] To date, no pet pesticides exposure studies have used socks to measure pet product residues transferred from the indoor environment. In the past, socks were more commonly used in conjunction with long sleeve shirts and pants as part of "whole body dosimeters" and often while wearing shoes.[26] Clothing offers an additional layer of dermal protection from chemicals. When socks or whole body dosimeters are used, a clothing penetration factor is included to estimate dermal dose. Studies investigating pesticide permeation through clothing estimated 8%–12% penetration.[31] A default of 10% is often used in evidence-based, non-dietary exposure assessment.[26, 31] Cotton socks worn indoors and the California Department of Food and Agriculture roller[26] both operate by contact transfer and represent available surface residues. Socks are particularly valuable as a three-dimensional matrix that incorporates foot surface area, and personal activity to measure transferability of surface residues from the indoor environment.

Three participants collected sock samples for two consecutive months following spot-on treatments of dogs as a preliminary investigation of the potential for fipronil to accumulate indoors with consecutive monthly use (as might occur in accord with label instructions). Fipronil levels on cotton socks were virtually the same during both months. Fipronil levels at the end of the second month were below those in the first month's pre-application sample. No evidence of excessive, i.e. additive, accumulation of fipronil or its derivatives in these residences was obtained during the two consecutive study periods (data not shown). The persistence of residues on indoor surfaces was not further investigated.

### *Urine biomonitoring*

The excretion of fipronil or its putative metabolites (the sulfone, sulfide, desulfinyl and destrifluoromethyl sulfinyl derivatives) was not established by urine biomonitoring. The biomonitoring aspect of this research is associated with considerable uncertainty. Low clothing or direct skin contact with fipronil in its emollient, prolonged low level potential contact, low dermal absorption, and the lipophilicity of fipronil and the derivatives available for these studies represented factors mitigating measurement of potential urine excretion. The persistence of fipronil on companion animals and in their environments shared with humans prompted us to question the extent of availability of fipronil and its derivatives for urine excretion.

Metabolism studies submitted to the USEPA[5] represent the most complete data available concerning the disposition of fipronil in mammals. Ring-$^{14}$C-Fipronil was administered by gavage to rats as single doses of 4 and 150 mg/kg

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and 4 mg/kg for 14 d. After 7 d significant amounts of radioactivity were present in carcass, gastrointestinal tract, liver, adrenals, and abdominal fat. Feces accounted for 45% to 75% of the administered dose. Urine contained 5% to 25% of the administered dose. There were no sex-linked differences in excretion. Major metabolites included acid-hydrolysable conjugates of ring-opened destrifluoromethylsulfinyl fipronil, fipronil sulfone, fipronil amide, and the parent insecticide (Fig. 1). The ring-opened metabolites represented most of the urine radioactivity and the sulfone conjugate was predominant among the other major metabolites.[4, 5] The major and virtually the only fipronil metabolite in mice was the sulfone formed following intraperitoneal administration of 2 mg/kg fipronil. Fipronil and the sulfone were found in brain, liver, kidney, fat, and feces. No polar metabolites not extractable with ethyl acetate were detected in aqueous extracts from mice.[7] The metabolic stability and storage of desulfinyl fipronil photoproduct was also reported in mice.[7]

Fipronil was rapidly absorbed and plasma levels declined during the first 15 to 20 h in patients who ingested large doses in suicide attempts.[34] Per oral dosages in these cases would represent exposures many orders of magnitude greater than those that might be associated with environmental exposures resulting from spot-on flea product use. Urinalyses were not performed. However, fipronil and the sulfone (mol ratio about 10:1) were measured in plasma and each decayed slowly after 20 h. The desulfinyl derivative was not found in plasma. In vitro CYP3A4 is the major enzyme responsible for fipronil metabolism in human liver microsomes. The oxidative microsomal activity of CYP3A4 was five times greater than that of CYP2C19 toward fipronil among 15 isoforms evaluated.[35] These findings are similar to those reported in mice and selected insects.

The recovery of fipronil from urine at 0.5 and 5 $\mu$g/L was 91% $\pm$ 6% and 84% $\pm$ 9%, respectively. The recoveries of the other derivatives at the lower and higher levels ranged 63% to 94% and 58% to 84%. The urine specimens were received in good condition and study staff was not aware of any factors that could have compromised the analysis of the fipronil biomarkers. The most telling observation was that the occurrence of biomarkers was sporadic and that pre-application levels and post-application measurements did not differ in most cases. The lack of consistency in the levels of urinary metabolites observed pre- and post usage may indicate that some urine specimens may have become contaminated during sampling, storage or analysis. Thus, quantitative biomonitoring results were not reported.

The earlier studies demonstrated the metabolism of fipronil to the corresponding sulfone[7, 34- 35] which has been measured as a conjugate in rat urine[5] together with other derivatives in lesser amounts.[4–5] Detailed studies following human exposures are lacking. Enterohepatic metabolism of fipronil and its primary lipophilic derivatives following low-level exposures resulting from the use of spot-on flea products may prolong elimination of fipronil derivatives resulting in amounts unmeasurable in urine biomonitoring.

The lack of a consistent measure of availability of absorbed dose from urine biomonitoring results did not allow a direct measure of exposure to indicate the persistence and distribution of fipronil and its lipophilic derivatives in residences. Several other important uncertainties contributed to variable results reported in these observational studies. These included the small number of participants that utilized the spot on product following label instructions on a larger number of dogs and cats of unique sizes, ages and activities. Compliance by participants with the basic requirements of the study was excellent; however, there is little doubt that sampling methods were more varied than they would have been under supervised experimental conditions. Although each participant provided animal and environmental samples that were useful to demonstrate the persistence and fate of fipronil, urine biomonitoring was not useful for exposure assessment to represent the collective human experience following use of the insecticide. The need for improved methods to assess the disposition and fate of very low levels of fipronil exposure in humans remains an important experimental objective, particularly given the demonstrated persistence of the insecticide and its lipophilic derivatives in the environment.

## Conclusion

Collectively, the results of this research demonstrate the time-dependent distribution and persistence of fipronil and its lipophilic derivatives in residences where spot-on treatments of dogs and cats have been applied. In the present studies the rapid movement of Frontline® fortified with a fluorescent marker in selected dogs gave graphic evidence of the movement of the product. These observations were coupled with longer-term measurements of fipronil and its key derivatives in hair clippings, brushed hair samples, and cotton gloves used to measure transferable residues.

Residues were available on the companion animals and in their indoor environments to the greatest extent during the first week following fipronil application of the spot-on product. Residues declined during the subsequent three weeks of study. Fipronil and its key lipophilic derivative residues in the indoor environment were measured using cotton cloths placed in areas frequented by the dogs and cats as well as through the use of cotton socks used by participants as direct dosimeters. Analysis of these samples reveals the time-dependent distribution and persistence of fipronil and its derivatives following spot-on treatments of companion animals in their residences. More convenient and sensitive analytical biomonitoring methods may be required to measure the extent of anticipated low-level human exposures resulting from the persistence of fipronil and its derivatives on pets and in their residences following spot-on flea control.

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## Acknowledgments

The enthusiastic assistance, cooperation and compliance of all study participants and their companion animals was essential to the completion of this research. Analytical standards were generously provided by BASF Corporation. This research of the University of California Citrus Experiment Station, Riverside was augmented by unrestricted gifts to the Regents of the University of California in support of the Personal Chemical Exposure Program. The registrant of Frontline® provided no direct or indirect support of this research.

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# Flea control failure? Myths and realities

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**Why is it that, despite the proliferation of research on their biology and control, fleas remain such a burden for companion animals and their owners? This review highlights a range of reasons for persistence and apparent treatment failures. It argues that a sustainable approach will require integrated pest management based upon a detailed understanding of the flea life cycle, targeting not only adult fleas but also the immature stages in the environment, combining several modes of control and limiting the risk of chemoresistance. Individual characteristics of the pet and its environment need to be considered. Control of fleas can be achieved, over a timescale of several months, if basic rules are respected.**

## Flea burdens: a never-ending story

Fleas are the most important insect ectoparasites of dogs and cats worldwide [1,2] and may readily infest humans. Beside direct pathogenic effects resulting from their obligate blood-feeding and the immuno-allergic skin response, fleas are also competent vectors for numerous pathogens, some of them being zoonotic – such as *Yersinia pestis* (plague), *Rickettsia typhi* (murine typhus), *Bartonella henselae* ('cat scratch disease' in humans), *Rickettsia felis* (flea spotted fever), and the tapeworm species *Dipylidium caninum* [3].

Recent studies have highlighted the high rate of flea infestation that is common in companion animals, varying between 12% and 47% in some European countries [4–6]. In most temperate areas, large variations in abundance occur during the year, with lower populations in winter, but usually without complete disappearance. Flea populations then increase from spring to fall. This has been reported in Spain, Italy, Hungary, and Germany [4–6] with peak infestation usually between June and August and lowest abundances between January and April [4,6]. In some countries, including Austria, Italy, Germany, and Spain, peak infestation rates of more than 70% have been reported [5]. Infestation rates may be highly variable from one year to another but also depend on location – rural or urban – and whether the pet has access to the outdoors.

Given the high prevalence of fleas with pathogenic and vector potential, effective control represents a major objective in small-animal veterinary medicine. The recent decade has seen the development of an increased number of insecticides dedicated to the control of flea infestation. These include topical and oral adulticides and insect growth regulators (IGRs). Nevertheless, flea infestations often persist or reoccur, even after the application of ostensibly potent flea-control products [7,8]. The reason why fleas remain a significant burden for companion animals and their owners, despite the proliferation of research on fleas and their control, is therefore an important question. The aim of the present Opinion article is to discuss possible reasons for the persistence of flea infestations, with a focus on the European situation where recent similar reviews are lacking. Most of the discussion presented here relates specifically to fleas of the genus *Ctenocephalides*.

Many factors influence the efficacy of a flea treatment strategy, and most of the time these factors are poorly understood by the main stakeholder, that is, the pet-owner. This is one of the main reasons for what appears to be treatment failure. Hence, a control strategy based on integrated management principles must include educating and promoting realistic expectations.

## The flea life cycle and persistent reinfestation from an environmental reservoir

The life-history strategies of parasites allow them to exploit their hosts effectively. Understanding both these strategies and the impact of parasites on their hosts is fundamental for developing appropriate control. Fleas are adapted to coexist with hosts that occupy discrete nest or bedding sites and which are usually only intermittently available; this is often compounded by long seasonal host absences and adverse environmental conditions in which they must be able to survive.

When hosts are present, a flea infestation is characterized by a long-lasting (up to 21 days) association between the adult flea and the host, during which multiple bloodmeals are taken, often several times per day [1,2,9,10].

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*Keywords:* flea control; companion animals; treatment failure; integrated management.

1471-4922/$ – see front matter
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When dropping off its host, the adult flea may only survive for 3–5 days. Only a relatively small proportion of fleas on pet animals probably move from one host to infest other animals, and the risk of one pet animal infesting another, in a waiting room or show for example, remains low; a recent study on cats indicated that only approximately 4% of infestations are acquired in this way [11]. Subsequent to host infestation and the first blood-meal, females begin egg-laying 36 h later, on average, depositing 20–30 eggs per day. The eggs fall from the fur of the host within a few hours, with approximately 70% being dislodged within 8 h [9,10]. Hatching and larval development occur in the nest or bedding material. This protected microhabitat combines moderate temperatures, high relative humidity, and a source of dried adult flea fecal blood [9,10]. In a domestic environment, appropriate conditions for larval survival may be found in a wide variety of locations where the pets are living, and the role of wooden floors and car upholstery is often underestimated. Having passed through three larval stages, the third-stage larva spins a silk cocoon in which it molts into a flea pupa and undergoes metamorphosis into a pre-emergence, pharate (cloaked) adult. The latter stage is highly resistant and is mechanically protected from the effects of insecticides [2]. Adults may then emerge from the cocoon immediately or, in the absence of appropriate stimuli, after several months. Once emerged, adult fleas must find a host and blood-feed to maintain the continuous infestation [9].

Hence, as a result of this life cycle, adult fleas on pets represent only the 'visible part of the iceberg'; indeed, only 1–5% of the flea population is represented by the adults on a host. The remaining 95% is hidden and is composed of difficult-to-find immature stages present in the environment. Furthermore, the presence of a highly resistant pupal stage and the pharate adult together provide considerable flexibility that allows persistence for extended periods during the absence of the host or rapid activity on the return of a host. Moreover, the rate of population growth may be high [9,12]. These factors together provide the most significant features explaining the majority of apparent control failures.

Optimal flea control needs to take into account these life-cycle characteristics. Adult fleas infesting the host must be eliminated, and further infestations by latent environmental stages should be prevented. As a result, with continuous treatment of a host, elimination of a flea population is likely to take an extended period of time. In field trials, on average 2–4 months are required to control flea populations, including environmental stages, from infested areas [5,13–15]. Modeling studies have shown that populations may even persist for up to 6 months in the absence of regular emergence stimuli, that is, the maximum lifespan of the pre-emerged fleas in cocoons [9,12]. These simulations demonstrate that the direct treatment of adult populations on the animal host using persistent insecticide prevents egg-laying and population growth, but continuous reinfestation by fleas from the environment is expected for as long as the environmental reservoir persists. The fleas observed on the animal during this period are not usually individuals that survived the treatment, but are newly emerged young adults that will be killed by the insecticide soon after they jump onto the host (Figure 1).

### External flea source as reservoir of reinfestation

Usually, the regular treatment of an infested host will be successful at controlling the fleas on the animal and in the immediate domestic environment. However, for animals that live in an open environment the role of external flea sources may be crucial in explaining further reinfestation [16]. This may be because the pet enters a contaminated area outside the household, or an untreated, contaminated host may visit the household. In the first case, although the presence of antiparasitic protection will decrease the probability of acquiring fleas, effective control will depend on the treatment cycle. Any failure in the continuity of the treatment will lead to reinfestation. External flea sources may include cars, other households, and parks where many owners are walking with their pets. The identification of these external contaminated areas is often difficult. In the second case, contamination of areas of the household suitable to support the flea life cycle may be due to the sporadic presence of infested animals (e.g., neighbor's cat, feral pets, or wild animals) contributing to the repletion of the environmental reservoir and limiting the clearance of the flea infestation [5,13–15].

### Persistent infestation by different flea species

Many flea species can infest companion animals – the cat flea, *Ctenocephalides felis felis*; the dog flea, *Ctenocephalides canis*; the human flea, *Pulex irritans*; and the hedgehog flea, *Archeopsylla erinacei* – are the most commonly identified. In Europe *C. felis felis* is the dominant species and is often recovered in more than 90% of cases on cats and dogs [2,7]. In some European countries *C. canis* may represent more than 50% of the fleas found on dogs [6]. Nevertheless, occasionally rodent fleas, flea species of small carnivores/insectivores, or birds fleas are observed, such as *Spilopsyllus cuniculi, Xenopsylla cheopis, Ceratophyllus gallinae*, and *Leptosylla segnis* [2,4,6]. Unless owners obtain appropriate expert identification of the flea, they are likely to attribute the presence of these 'exotic' species on their animal to domestic control failure.

### Persistent infestation due to owner-related behavior

One of the main reasons for pet owner-related flea-control failure is lack of compliance [7]. The most common causes include: (i) infrequent product application or a treatment interval extended to 8–9 weeks, noting that most flea products licensed today have a duration of activity of 4–6 weeks; (ii) treatment conducted only when fleas are seen on the animal; (iii) failure to treat all of the animals present in the same house; and (iv) suspension of treatment in winter even though fleas are still active. Additional causes may include the application of an incorrect dosage, linked to the use of an inappropriate size-related dosage, especially on growing puppies or large cats, or incorrect administration technique, such as application of a topical product on the hair rather than onto the skin. Some oral products need to be given along with food to permit optimal absorption. Excessive washing or frequent water immersion (bathing or swimming), as well as application to a wet



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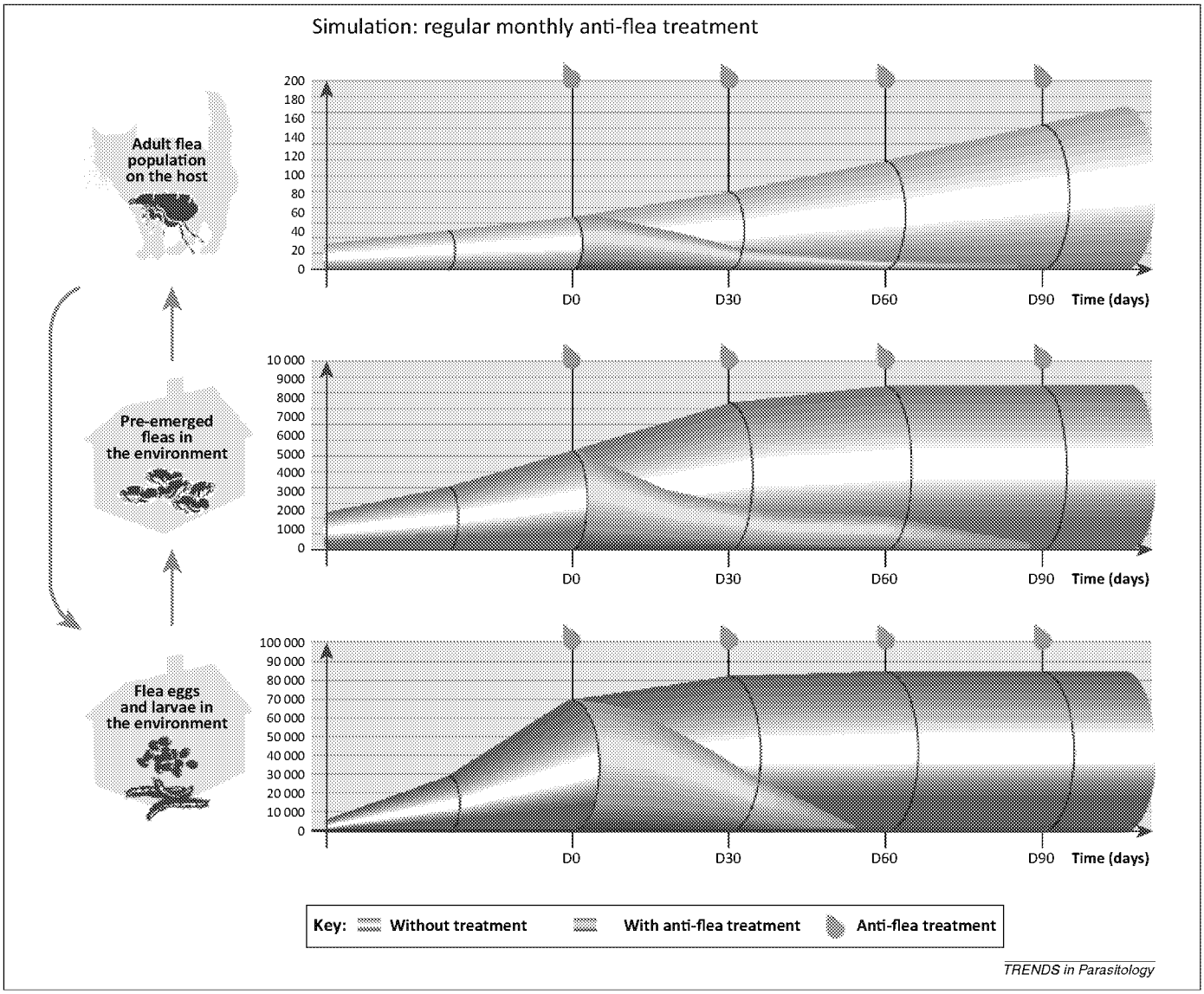


**Figure 1.** Dynamics of a flea population over time. Based on mathematical modeling [12], the flea populations on the host and in the environment are represented graphically over a number of days (*x* axis) in regards to the size of the population (*y* axis). The starting point reflects a mild household infestation with no hidden reservoir. Each panel shows the population with no treatment (grey line) and changes after four successive treatments at monthly intervals (blue line). Top panel, adults on the host; middle panel, pre-emerged adults; lower panel, eggs and larvae.

coat, will also jeopardize the efficiency of topical products. Insecticides with a topical diffusion – skin translocation – are more susceptible to repetitive water immersion or shampooing. Even where formulations explicitly incorporate water resistance, weekly or daily contact with water would result in a decrease of efficacy [7,8]. Most of these mistakes are related to poor adherence to the instructions on the label, and emphasize the importance of education and the provision of clear information to pet-owners.

## Persistent infestation related to product characteristics

A wide range of molecules and products are available for flea control [17]. Their mode of action and mode of application is summarized in Table 1 [17]. These licensed products must reach standards of efficacy determined by pharmaceutical regulation worldwide [European Medicine Agency (EMA) in Europe]. Following these guidelines, the efficacy of a drug against fleas must reach at least 95%, 48 h post-infestation in repeated controlled studies (see http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004343.pdf). However, in addition to licensed products, a wide range of preparations are based on botanical compounds or other 'natural' sources which are used as alternatives for flea control; for example, pyrethrin, d-limonene, Neem oil, silica dust, and diatomaceous earth [18]. In most cases the efficacy of these products has not been clearly demonstrated. Neem oil was shown to induce a high level of mortality in fleas for one week after application [19], but few published results are available for most other compounds. In addition, the safety of these products has not been fully tested; acute toxicity after application of a d-limonene-based insecticidal shampoo in a cat has been described [20].

Two types of insecticides are available to control flea populations. Conventional neurotoxic insecticides act on the nervous system of the flea and are administered either topically or orally to the pets. They target adult fleas on the



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**Table 1. Molecules used for flea control in veterinary medicine[a]**

| Chemical group | Molecules | Mode of action | Mode of application |
|---|---|---|---|
| **Adulticides** | | | |
| Cyclodiene Organochlorines | Lindane | Fixation on sodium ion channels; stimulation of $Na^+$ entry in nerve cells; hyperexcitation | No longer marketed in Europe and North America |
| Organophosphates | Diazinon, fenthion | Cholinesterase inhibitors; stimulation of nerve cells | Collar, external solution |
| Carbamates | Carbaryl, propoxur | Cholinesterase inhibitors; stimulation of nerve cells | Dust, collar, spray |
| Pyrethroids | Permethrin, deltamethrin, flumethrin | Fixation on sodium channels; stimulation of $Na^+$ entry in nerve cells; hyperexcitation of nerve cells | Spray, spot on, collar, shampoo, fogger, environmental spray |
| Phenylpyrazoles | Fipronil, pyriprole | Fixation on both GABA and glutamate receptors of chloride ions channels; blockage of $Cl^-$ entry; hyperexcitation of nerve cells. | Spray, spot on |
| Chloronicotinyl-nitroguanidines, neonicotinoids | Imidacloprid, dinotefuran, nitenpyram | Stimulation of nicotinic acetylcholine receptors; stimulation of postsynaptic neurons | Spot on, collar |
| Spinosyns macrocyclic lactones | Spinosad, spinetoram | Stimulation of nicotinic acetylcholine receptors; stimulation of postsynaptic neurons | Oral, spot on |
| Oxadiazine | Indoxacarb | Sodium channel antagonist; paralysis and death | Spot on |
| Semicarbazone | Metaflumizone | Sodium channel antagonist; paralysis and death | Spot on |
| Macrocyclic lactones (avermectin/milbemycin) | Selamectin | Fixation on glutamate receptors; stimulation of $Cl^-$ entry; inhibition of nerve cell activity | Spot on |
| Isoxazoline | Afoxolaner, fluralaner | Fixation on GABA and glutamate receptors of chloride ion channels of the synapses; blockage of $Cl^-$ entry; hyperexcitation of nerve cells | Oral |
| **IGR (insect growth regulators)** | | | |
| Juvenile hormone analogs | *S*-methoprene, pyriproxyfen | Decrease reproductive output; reduced egg hatch; mortality at last molt from larva to pupa stage | Spot on, fogger, environmental spray |
| Organofluorines – benzoylureas | Lufenuron, flufenoxuron | Chitin synthetase inhibitor; inhibits egg hatching; induces mortality during molting | Oral, injection, fogger, environmental spray |

[a]Abbreviation: GABA, γ-amino butyric acid.

host or possibly larval stages that consume the skin debris from a treated animal. Insect growth regulators (IGRs), conversely, target only immature stages by interrupting their development process. Adult fleas that come into contact with the IGR will not be directly affected, but their offspring will be unable to complete development, and eventually the population will be eliminated [17]. The use of a neurotoxic insecticide only, IGR only, or a combination of both, will have different effects on the overall flea population. With the use of an adulticide only, the decrease in the concentration of the active ingredient over time may allow the survival of some fleas such that some of them are able to lay eggs before dying. This may lead to a continued contamination of the environment if the interval between two treatments is too long. By contrast, although the use of an IGR only would provide progressive control of the flea populations, it would also allow a constant reinfestation by fleas emerging from the pupal reservoir, and this would continue until the pupal reservoir is completely depleted, which may be several months after treatment begins.

In addition to the different molecules and the specificity of their modes of action, considering the mode of application (e.g., spray, spot-on, tablet, or collar) of the insecticide products is of utmost importance because this is also likely to have an impact on owner compliance. The mode of application influences the duration of efficacy of the product. Thus the schedule of treatment and the interval between successive applications needed for the control of the flea population is crucial. Most existing products have a period of activity of about 1 month. Longer-lasting efficacy of several months may be obtained with collars or long-acting oral formulations. Although bringing convenience, in some instances long-lasting drugs may also impair owner compliance by increasing the timing between two administrations and limiting the awareness of the need for continuous prevention during the flea season. Each situation requires a specific solution and, for optimal compliance, the product used should be carefully selected depending on the needs of each pet-owner and the activities of the pet.

## Is resistance against the antiparasitic drugs a major factor of persistent reinfestation?

Updated knowledge on insecticide and acaricide resistance was recently reviewed by Cole and Dryden [7]. As defined by the Insecticide Resistance Action Committee (IRAC), resistance results from 'a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species' (see http://www.irac-online.org/about/resistance/). In contrast to resistance, tolerance reflects a natural tendency rather than a selection pressure: natural insect populations of the same species may have a range of susceptibility or tolerance to a given insecticide [7]. Both resistance and tolerance to diverse insecticides have been described in *C. felis* fleas. Although resistance to old insecticides including cyclodienes, carbamates, organophosphates, and pyrethroids has been demonstrated, especially in US strains [21,22], in contrast to natural variation in susceptibility,



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true resistance against modern adulticides in field strains has not (e.g., imidacloprid, fipronil, pyriprole, metaflumizone, selamectin, spinosad, etc.). However, in practical terms, the differentiation between natural variation in susceptibility or resistance is difficult to determine, as demonstrated by the KS1 strain of *C. felis* collected from dogs and cats in Kansas in 1990, which shows either resistance or naturally low susceptibility to carbaryl, chlorpyrifos, fenthion, fipronil, imidacloprid, permethrin, pyrethrins, and spinosad [7]. Because resistance selection is certainly possible in fleas, it is crucial that we attempt to maintain the efficacy of the current therapeutic agents, for example by the complementary use of IGRs to sterilize flea populations and the use of a treatment schedule that avoids under-dosed animals. When a veterinary practitioner or pet-owner notes an apparent failure of insecticide efficacy, the cause is most probably a result of treatment deficiency rather than resistance [7].

## New approaches for integrated flea control and perspectives

Integrated pest management (IPM) is an approach originally developed in crop protection that aims to implement a decision-based process involving coordinated use of multiple tactics for optimizing the control of all classes of pests, for instance, insects, pathogens, weeds, or vertebrates, in an ecologically and economically sound manner [23]. The need to use such approaches for flea control is widely accepted [7] but is not easily implemented. Application of IPM to flea control will require appropriate consideration of the following: (i) flea ecology, including seasonality, cycles, and stages, in terms of period, length, and interval of treatment and choice of the targeted stages, and (ii) the use of a combination of several measures to enhance control of the global populations and limit the risk of emergence of resistance. The latter will include chemical measures targeting both adult and immature stages and mechanical measures that contribute to depletion of the environmental reservoir. Education of all the people involved and promotion of realistic owner expectations are crucial [7,8]. Incorporating an understanding of the length of time required to resolve any individual flea problem, and awareness that this is governed by the source and reason for reinfestation, is an integral part of this process. This requires the following questions to be addressed: (i) where is the reservoir of pupae; (ii) what was the population density in the environment at the onset of control; and (iii) what is the specific phenology of flea activity in the given area? In the latter case, the phenology may be year-round, as in Mediterranean countries, or strongly seasonal as in temperate climates.

## Concluding remarks

Regular treatment of the hosts – cats and dogs – can break the life cycle of fleas and provide control if some fundamental rules are respected: effective application, correct treatment intervals, and prevention of reinfection from new sources of fleas (Box 1). With intensive flea pressure, even minor lapses in compliance can result in the impression of product failure. The development of an IPM approach for fleas is a valuable objective of best practice. The approach must include targeting not only the visible part of the infestation, that is, the adult fleas, but also the immature stages by combining several modes of control and limiting the risk of chemoresistance. Last, detailed consideration of the individual characteristics of the animal and its environment are essential for effective flea IPM.

**Box 1. Guidelines for optimal flea control**

Key criteria for an optimal control strategy and for avoiding recurrent flea infestation [2,7].

*Understand the origin of the flea infestation*

The epidemiological context must be investigated. This includes collection of information on the number of animals in the household, their access to open outdoors areas, and the potential presence of external sources.

*Develop an integrated flea-control strategy tailored to each context*

The established program must target both on-host adult fleas and environmental immature stages, and be adapted to the profile, habits, and behavior of the pet-owner and animals. This should include:

(i) Mechanical control of environmental stages will include vacuuming, washing pet bedding, and cleaning all areas where eggs that may harbor eggs.
(ii) Use appropriate anti-flea, veterinary registered products that provide effective flea adulticide and environmental life-stage control. Avoid the use of non-labeled products.
(iii) Select an appropriate application mode. If animals are regularly shampooed or present with skin disease, oral treatment may be preferred. Where there is a risk for coinfestation by other parasites, a combination product may be recommended to limit the number of treatments required.
(iv) Choose active ingredients or combinations with consideration of the risk for infestation or bites by other ectoparasites such as ticks or mosquitoes.
(v) For the choice of insecticidal molecule, consider specific safety concerns related to cats versus dogs or cats living with dogs.
(vi) When handling the animal is difficult, select the easiest mode of application.
(vii) Adapt the schedule of treatment and the interval between two treatments to guarantee the highest compliance.

*Make sure that the pet-owner clearly understands the issues*

To guarantee the sustainability of the strategy, it is essential to spend time educating direct stakeholders (e.g., veterinary staff and pet-owners) about flea biology and promoting realistic owner expectations; the presence of fleas on a treated animal is not unusual, and it may take more than a month to deplete the environmental reservoir.

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Message

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**Subject**: Pesticide Program Update: EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pet

# EPA Pesticide Program Updates

*From EPA's Office of Pesticide Programs*

*www.epa.gov/pesticides*

January 4, 2017

## In This Update:

### EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pets

EPA has finalized the human health risk assessment of tetrachlorvinphos (TCVP). TCVP is an organophosphate insecticide used to control fleas, ticks, and other pests on and around pets and livestock. It is used in residential products like pet collars.

Through the publication of the revised human health risk assessment and related documents, we are addressing a 2009 Natural Resource Defense Council (NRDC) petition.

This risk assessment identified potential risks to people, including children, in residential settings and to certain workers applying TCVP, which exceed the Agency's level of concern.

The Agency has contacted the pesticide manufacturers to initiate discussions with them to reduce exposure and resolve potential risks identified in the human health risk assessment. The Agency will issue a Proposed Decision in 2017 for public comment. Until that time, it is important to follow label instructions on proper use of pesticide products.

We advise consumers to take certain precautions when handling TCVP products in residential areas. These precautions are listed on TCVP product labels, including:

- not allowing children to play with TCVP pet collar products,
- keeping TCVP spray and powder products out of reach of children, and
- washing hands thoroughly with soap and water after handling.

To view TCVP's human health risk assessment and other registration review documents, visit regulations.gov, docket number EPA-HQ-OPP-2008-0316.

More information on:

- tetrachlorvinphos
- protecting your pets form fleas and ticks
- reducing your child's chances of pesticide poisoning

EPA distributes its Pesticide Program Updates to external stakeholders and citizens who have expressed an interest in the agency's pesticide program activities and decisions. This update service is part of EPA's continuing effort to improve public access to federal pesticide information.

For general questions about pesticides and pesticide poisoning prevention, contact the National Pesticide Information Center (NPIC), by email at npic@ace.orst.edu or, by visiting http://npic.orst.edu.

For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: http://www.epa.gov/pesticides.

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This email was sent to keigwin.richard@epa.gov using GovDelivery, on behalf of: U.S. EPA Office of Chemical Safety and Pollution Prevention · 408 St. Peter Street, Suite 600 · Saint Paul, MN 55102 · 1-800-439-1420

Message

**From**: Lydon, Maureen [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=A8B57B97110045788347E95D63D0F140-MLYDON]
**Sent**: 8/18/2016 12:26:22 PM
**To**: Dave Johnson [davejohn@johnsonmgt.com]; 'Rhonda Bichsel' [rhondab@johnsonmgt.com]
**CC**: Crowley, Matthew [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=239604484b0a44579788691f5765302f-Matthew T Crowley]; Keigwin, Richard [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=151baabb6a2246a3a312f12a706c0a05-Richard P Keigwin Jr]
**Subject**: Copy for AHETF - Meeting Minutes from July HSRB meeting
**Attachments**: HSRB July 2016 Meeting Minutes CERTIFIED Final.pdf

Hello Dave and Rhonda,

Hope this note finds you well.

Last evening, EPA's Office of the Science Advisor (OSA) issued the attached minutes from the July HSRB meeting. We wanted you to have a copy.

The HSRB's next step will be for the HSRB members to reach agreement on their final report from the meeting. After they do that, OSA will post the minutes and final report on the HSRB website.

Thanks,
Maureen

Maureen Lydon
Human Research Ethics Review Officer
Office of the Director
Office of Pesticide Programs, U.S. EPA
703-347-0440, Potomac Yard South 12613

Message

**From**: RAB57 - HED/OPP [no-reply@sharepointonline.com]
**Sent**: 11/3/2016 12:42:27 PM
**To**: Metzger, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=655bc1c05459419d8bb3ba9a16568c3f-Michael S. Metzger]
**Subject**: RAB57 Peer Review - TCVP Revised ORE has been assigned to you

RAB57 - HED/OPP

# ***TCVP Revised ORE*** has been assigned to you

Modify my alert settings | View TCVP Revised ORE | View RAB57 Peer Review | Mobile View

| | |
|---|---|
| **Title:** | TCVP Revised ORE |
| **Predecessors:** | |
| **Priority:** | (2) Normal |
| **Task Status:** | Not Started |
| **% Complete:** | 0% |
| **Document Created By:** | Lowe, Kelly |
| **Assigned To:** | Britton, Wade; Metzger, Michael; Drew, Danette; Habiba, Uma |
| **Description:** | |
| **Start Date:** | |
| **Due Date:** | |
| **Completed:** | No |
| **Peer Review Type:** | ORE Memos for Branch QA-QC |

Last Modified 11/3/2016 8:42 AM by Lowe, Kelly

Message

**From**: EPA Pesticides Programs [oppt.epa@public.govdelivery.com]
**Sent**: 1/4/2017 7:17:31 PM
**To**: Metzger, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=655bc1c05459419d8bb3ba9a16568c3f-Michael S. Metzger]
**Subject**: Pesticide Program Update: EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pet

# EPA Pesticide Program Updates

*From EPA's Office of Pesticide Programs*

*www.epa.gov/pesticides*

January 4, 2017

## In This Update:

### EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pets

EPA has finalized the human health risk assessment of tetrachlorvinphos (TCVP). TCVP is an organophosphate insecticide used to control fleas, ticks, and other pests on and around pets and livestock. It is used in residential products like pet collars.

Through the publication of the revised human health risk assessment and related documents, we are addressing a 2009 Natural Resource Defense Council (NRDC) petition.

This risk assessment identified potential risks to people, including children, in residential settings and to certain workers applying TCVP, which exceed the Agency's level of concern.

The Agency has contacted the pesticide manufacturers to initiate discussions with them to reduce exposure and resolve potential risks identified in the human health risk assessment. The Agency will issue a Proposed Decision in 2017 for public comment. Until that time, it is important to follow label instructions on proper use of pesticide products.

We advise consumers to take certain precautions when handling TCVP products in residential areas. These precautions are listed on TCVP product labels, including:

- not allowing children to play with TCVP pet collar products,
- keeping TCVP spray and powder products out of reach of children, and
- washing hands thoroughly with soap and water after handling.

To view TCVP's human health risk assessment and other registration review documents, visit regulations.gov, docket number EPA-HQ-OPP-2008-0316.

More information on:

- tetrachlorvinphos
- protecting your pets form fleas and ticks
- reducing your child's chances of pesticide poisoning

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For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: http://www.epa.gov/pesticides.

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Message

**From**: RAB57 - HED/OPP [no-reply@sharepointonline.com]
**Sent**: 10/11/2016 6:27:59 PM
**To**: Metzger, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=655bc1c05459419d8bb3ba9a16568c3f-Michael S. Metzger]
**Subject**: RAB57 Peer Review - TCVP revised RA has been assigned to you

RAB57 - HED/OPP

# ***TCVP revised RA*** has been assigned to you

Modify my alert settings | View TCVP revised RA | View RAB57 Peer Review | Mobile View

| | |
|---|---|
| **Title:** | TCVP revised RA |
| **Predecessors:** | |
| **Priority:** | (2) Normal |
| **Task Status:** | Not Started |
| **% Complete:** | 0% |
| **Document Created By:** | Drew, Danette |
| **Assigned To:** | Britton, Wade; Taylor, Linda; Metzger, Michael; Habiba, Uma; Lowe, Kelly |
| **Description:** | Master document for Team inputs |
| **Start Date:** | 10/11/2016 |
| **Due Date:** | 10/21/2016 |
| **Completed:** | No |
| **Peer Review Type:** | Risk Assessment Documents for Branch QA-QC |

Last Modified 10/11/2016 2:27 PM by Drew, Danette

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/9/2017 7:27:45 PM
**To**: Maxcy Nolan Personal Matters / Ex. 6
**CC**: maxcypiii@gmail.com; maxcypnolaniv@gmail.com; Nguyen, Khue [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53463f4f956d4772a6ada2f68debfcb8-Nguyen, Khue]
**Subject**: RE: tetrachlorvinphos

Hi Nolan,

Please discard the attachment to the previous email. Regarding the information related to tetrachlorvinphos, please submit any information that you may have via email.

Thank you,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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**From:** Parker, James
**Sent:** Thursday, February 09, 2017 1:58 PM
**To:** 'Maxcy Nolan' Personal Matters / Ex. 6
**Cc:** maxcypiii@gmail.com; maxcypnolaniv@gmail.com; Nguyen, Khue <Nguyen.Khue@epa.gov>
**Subject:** RE: tetrachlorvinphos

Hi Nolan,

The Agency is currently in the process of developing a Proposed Interim Decision for the pesticidal uses of tetrachlorvinphos. Therefore, any use, benefits, and/or alternatives information that you can provide would be greatly appreciated. If you have any questions, please feel free to contact me or Khue Nguyen.

James Parker
703-306-0496

**From:** Maxcy Nolan [Personal Matters / Ex. 6
**Sent:** Wednesday, February 08, 2017 3:26 PM
**To:** Parker, James <Parker.James@epa.gov>
**Cc:** Personal Matters / Ex. 6
**Subject:** tetrachlorvinphos

I understand EPA is requesting information about tetrachlorvinphos. I would like to provide information about the uses and need for tetrachlorvinphos to be available to control arthropods of veterinary importance. Please provide me the information necessary to provide EPA with this information. Thank you for your help.

Maxcy P. Nolan, Jr., Ph.D.
NIPCAM GROUP
Personal Matters / Ex. 6

Message

**From**: Doug Spilker [doug.spilker@bayer.com]
**Sent**: 1/26/2017 6:48:37 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]
**Subject**: RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment (MRID 48773401 vs. 48773401a?

Thanks, I will send onto my colleagues, to see what they make of this. Bruce Bernard is off until Tuesday – maybe he can shed some light on this.

Best regards,

Doug

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs

Bayer: Science For A Better Life

Bayer U.S. LLC
Animal Health R&D, Regulatory Affairs
P.O. Box 390
Shawnee, KS 66201
USA
Tel: +1 913 268 2751
Mobile: +1 816 506 3102

E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Thursday, January 26, 2017 12:45 PM
**To:** Doug Spilker
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment (MRID 48773401 vs. 48773401a?

Hi Doug,

An acute CCA study report was found embedded in the repeat CCA study report (MRID 48773401) which was discovered when we were working on the repeat CCA DER. That acute CCA study should have been submitted as a separate study, so that it would have been assigned a separate MRID#. However, since the acute study was submitted as part of the repeat report, it had to have the same MRID#. The acute study was assigned MRID 48773401a.

I hope this information is helpful,

James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469

Parker.james@epa.gov

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**From:** Doug Spilker [mailto:doug.spilker@bayer.com]
**Sent:** Thursday, January 26, 2017 9:56 AM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment (MRID 48773401 vs. 48773401a?

Hi James, Thanks for quick response. I do need some help with something else.

In the recent HHRA, the Benchmark Dose (BMD) was recalculated using information in MRID 48773401a. However, we are not sure what that document really is. We have the DER for MRID 48773401, but not **48773401a** ( see attached from HHRA). According to our consultant, Bruce Bernard, he made several additional submissions to the CCA study, but is unable to cross-reference them with this MRID number or any of his paperwork. Furthermore, it does not show up in NPIRS.

Could you please see what you can find out about this document (48773401a) – e.g. title, study number, etc. - and whether a specific DER is available?

Thanks for your help.

Best regards,

Doug

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs

Bayer: Science For A Better Life

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Animal Health R&D, Regulatory Affairs
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Tel: +1 913 268 2751
Mobile: +1 816 506 3102

E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Thursday, January 26, 2017 7:55 AM
**To:** Doug Spilker
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Hi Doug,

Thank you for your inquiry regarding language on page 5 of the HHRA which identifies the need for a mouse micronucleus assay (GLN 870.5395). We do not intend to issue another DCI for the registration review of TCVP because the registration review occupational and residential exposure assessment has already been finalized. However, because a data gap has been identified, it is possible that these data may be required during the next round of registration view or to support a new use or registration. Again, at this time we do not have any plans to issue another registration review DCI for TCVP.

James P.

James Parker, M.S.
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Parker.james@epa.gov

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**From:** Doug Spilker [mailto:doug.spilker@bayer.com]
**Sent:** Wednesday, January 25, 2017 4:06 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Thanks, James.

I do have a question. On page 5 of the HHRA it says that a follow-up mouse micronucleus assay is required. Would an official DCI be issued for this, and if so, when would it come? Just thinking about budgets.

Best regards,
Doug

Douglas A. Spilker, Ph.D.
Manager, EPA Regulatory Affairs

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Tel: +1 913 268 2751
Mobile: +1 816 506 3102

E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Wednesday, January 25, 2017 12:03 PM
**To:** Doug Spilker
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Hi Doug,

Thank you for following-up with me, the tetrachlorvinphos team will be contacting the tetrachlorvinphos technical registrants in the near future to discuss what mitigation will be needed in order resolve anticipated risks resulting from the pesticidal use of tetrachlorvinphos. If in the meantime you or your team develop any questions or concerns, please feel free to contact me.

Best Regards,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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---

**From:** Doug Spilker [mailto:doug.spilker@bayer.com]
**Sent:** Wednesday, January 25, 2017 12:20 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Hi James,

Thanks for the heads-up on this. We have been evaluating the HHRA and the agency's responses to our comments. I was curious - **what is the next step, and when would that happen?**

We do not have any comments or questions at this moment but our risk assessors are still looking at these documents.

Best regards,

Doug

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Manager, EPA Regulatory Affairs

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Tel: +1 913 268 2751
Mobile: +1 816 506 3102

E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Thursday, December 29, 2016 12:06 PM
**Subject:** Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

The Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment for Registration Review has been finalized and is in the process of being posted to the TCVP registration review docket at regulations.gov (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2008-0316). Although the revised risk assessment does not yet appear to be posted to the docket, I expect that it will be in the docket later today or tomorrow. If you have any questions or concerns, please feel free to contact me.

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**From**: Doug Spilker [doug.spilker@bayer.com]
**Sent**: 1/26/2017 2:56:19 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]
**Subject**: RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment (MRID 48773401 vs. 48773401a?
**Attachments**: 20170126081903005.pdf

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Best regards,

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Best Regards,
James P.

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Chemical Review Manager
Pesticide Re-evaluation Division
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E-mail: doug.spilker@bayer.com
Web: http://www.bayer.com

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**Subject:** Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

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James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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Message

**From**: Bruce Bernard [bernard@sra-intl.com]
**Sent**: 10/10/2016 1:24:21 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]
**Subject**: TCVP Aerobic Soil Metabolism
**Attachments**: 161005 Complete ltr to EPA Resp to Crit.pdf

**Importance**: High

Dear James,

Attached please find the TCVP Task Force responses to EPA's comments on the above identified study.

Thank you for handling this matter.

Sincerely,

Bruce Bernard

Message

**From**: Bruce Bernard [bernard@sra-intl.com]
**Sent**: 8/31/2016 12:54:18 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]
**Subject**: RE: Document request - TCVP

Dear James,

Thank you so much…this is exactly what I was looking for.

Best wishes,

Bruce B.

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Wednesday, August 31, 2016 7:57 AM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Subject:** RE: Document request - TCVP

Hi Bruce,

It's good to hear from you again. In reference to the aerobic soil metabolism study (GLN 835.4100), the most recent waiver response was sent out back in March 2011. I have attached the associated waiver request and agency response above.

I hope this information is helpful,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Tuesday, August 30, 2016 5:38 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** Document request - TCVP
**Importance:** High

Hello James,

It has been a long time; hope you and your family are well.

I am writing to you about Tetrachlorvinphos (TCVP, Rabon). A LONG time ago, shortly after the Generic DCI was issued (I think in 2011), I put in a WAIVER REQUEST for a study (AEROBIC SOIL METABOLISM, 835.4100). The response from EPA was a denial of the waiver request for the ENTIRE STUDY, but EPA did give me a wavier for TWO of the FOUR soil types (i.e. we had to performed 2 soils instead of 4).

Would you be so kind as to send me a copy of that correspondence?

Thanking you ever so much.

Sincerely,

Bruce Bernard
202.422.5920

Message

**From**: Doug Spilker [doug.spilker@bayer.com]
**Sent**: 7/22/2016 7:40:03 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]
**Subject**: TCVP Question

Hi James,

Hope you are staying cool! It is so hot in KC, it was 80F at 6am this morning.

As you are likely aware, we inherited the TCVP Task Force arrangement with Hartz and SRA International (Bruce Bernard). It has worked okay, but the arrangement is a little awkward with SRA International; we at Bayer commonly work directly with EPA and not through a consultant, since we have our own regulatory group. I have never felt like I was always getting copies of all the correspondence to/from the Agency. You have done very good lately, but I don't really have a historical file that goes back very far. We did not get much from KMG when we bought their products.

Now my question: How thick is the Regulatory "Jacket" containing all of the PRED correspondence for TCVP? Might it be something that I could request a copy of, by paying a per page charge? If it is too thick, then maybe I consider just since the last DCI, or other suggestion by you.

Your thoughts would be appreciated.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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Message

**From**: Doug Spilker [doug.spilker@bayer.com]
**Sent**: 7/19/2016 2:38:09 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]
**Subject**: RE: Tetrachlorvinphos (TCVP) Soil ECM/ILV DER (MRID 49334401)

Thanks.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Tuesday, July 19, 2016 8:54 AM
**To:** Doug Spilker; Bruce Bernard
**Subject:** Tetrachlorvinphos (TCVP) Soil ECM/ILV DER (MRID 49334401)

Please find attached above, the updated data evaluation record and transmittal memo for the TCVP Soil ECM/ILV study (49334401) and supplemental data (49846101), which have been reviewed by the Agency and classified as Acceptable. If you have any questions or concerns, please feel free to contact me.

Best Regards,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 10/3/2016 12:41:16 PM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: TCVP

Hi Bruce,

In reference to the EPA's evaluation of the Aerobic Metabolism study, please feel free to submit a "response" directly to me via email.

Best Regards,
James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Friday, September 30, 2016 11:36 AM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** TCVP

Dear James,

Hope you are well.

I am going to submit a 'response' to the EPA evaluation of the Aerobic Metabolism study.

May I do this directly to you or do I have to go the 'formal' route, submission form, etc.?

Best wishes,

Bruce

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 7/19/2016 1:54:10 PM
**To**: Doug Spilker [doug.spilker@bayer.com]; Bruce Bernard [bernard@sra-intl.com]
**Subject**: Tetrachlorvinphos (TCVP) Soil ECM/ILV DER (MRID 49334401)
**Attachments**: 083702_431931_DER-Memo_07-14-16.pdf; 083702_49334401_DER-Fate_850.6100_06-20-16.pdf

Please find attached above, the updated data evaluation record and transmittal memo for the TCVP Soil ECM/ILV study (49334401) and supplemental data (49846101), which have been reviewed by the Agency and classified as Acceptable. If you have any questions or concerns, please feel free to contact me.

Best Regards,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

**PC Code: 083702**
**DP Barcode: 431931**

**MEMORANDUM** July 14, 2016

**SUBJECT:** **TCVP:** Transmittal of Data Evaluation Records (DERs) for Environmental Fate Studies.

**TO:** James Parker, Chemical Review Manager
Tom Moriarty, Team Leader
RMIB II / PRD (7508P)

**FROM:** Chuck Peck, Environmental Engineer
ERB IV / EFED (7507P)
2016.07.14
09:46:14 -04'00'

**REVIEWED BY:** Jim Carleton, Ph.D., Senior Fate Scientist
ERB IV / EFED (7507P)
JAMES CARLETON
Digitally signed by JAMES CARLETON
DN: c=US, o=U.S. Government, ou=USEPA, ou=Staff, cn=JAMES CARLETON, dnQualifier=0000001907
Date: 2016.07.14 12:42:52 -04'00'

**APPROVED BY:** Jean Holmes, D.V.M., MPH Branch Chief
ERB IV / EFED (7507P)
JEAN HOLMES
Digitally signed by JEAN HOLMES
DN: c=US, o=U.S. Government, ou=USEPA, ou=Staff, cn=JEAN HOLMES, dnQualifier=0000005813
Date: 2016.07.14 12:24:52 -04'00'

This memo is to inform you that one (1) DER amendment for TCVP has been finalized. One (1) electronic file is associated with the finalized DER. The study MRID and classification are listed in **Table 1** below.

**Table 1. MRIDs and Classifications for Environmental Fate Studies of Acrolein.**

| MRID | Study Type | DER Electronic File Name | Study Classification |
|---|---|---|---|
| 49334401/ 49846101 | Soil ECM/ILV | 083702_49334401_850.6100_06-15-16.pdf | Acceptable |

MRID 49334401 was initially classified as unacceptable, but upgradeable in November 2015. Subsequent information was submitted to address the deficiencies of the study and make it acceptable.

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 8/31/2016 11:57:20 AM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: Document request - TCVP
**Attachments**: TCVP Hydrolysis + phosphate mty waiver response 3.14.11.pdf; TCVP TF Data Waiver Request for Hydrolysis 2.24.11.pdf

Hi Bruce,

It's good to hear from you again. In reference to the aerobic soil metabolism study (GLN 835.4100), the most recent waiver response was sent out back in March 2011. I have attached the associated waiver request and agency response above.

I hope this information is helpful,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Tuesday, August 30, 2016 5:38 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** Document request - TCVP
**Importance:** High

Hello James,

It has been a long time; hope you and your family are well.

I am writing to you about Tetrachlorvinphos (TCVP, Rabon). A LONG time ago, shortly after the Generic DCI was issued (I think in 2011), I put in a WAIVER REQUEST for a study (AEROBIC SOIL METABOLISM, 835.4100). The response from

EPA was a denial of the waiver request for the ENTIRE STUDY, but EPA did give me a wavier for TWO of the FOUR soil types (i.e. we had to performed 2 soils instead of 4).

Would you be so kind as to send me a copy of that correspondence?

Thanking you ever so much.

Sincerely,

Bruce Bernard
202.422.5920

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/6/2017 5:07:33 PM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: TCVP

The science team referred to the sub-study as MRID 48773401a to differentiate it from the primary study because it (like the primary study) was assigned MRID 48773401 when submitted to the Agency. Again, the data referred to as 48773401a was embedded within the primary data submission (MRID 48773401). In order for a new MRID number to be assigned to the embedded study, it would have needed to be submitted separately.

James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Monday, February 06, 2017 11:50 AM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

I don't understand. Didn't you say that in reviewing MRID 48773401, they found a second study inside and gave it the MRID 48773401a?

B

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Monday, February 6, 2017 11:48 AM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Subject:** RE: TCVP

Bruce,

Our processing group only shows that we received MRID 48773400/01. There is no separate MRID number for 48773401a.

James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Monday, February 06, 2017 11:44 AM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

Dear James,

Thank you for the cover sheet from the 11day CCA study.

Do you have the cover sheet for the MRID 48773401a?

Bruce

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Monday, February 6, 2017 10:06 AM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Subject:** RE: TCVP

Hi Bruce,

The transmittal sheet associated with MRID #48773401 is attached above. If you'd still like for me to mail you the associated CD, please send me your mailing address.

Best Regards,
James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Monday, February 06, 2017 9:15 AM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

James,

THANK YOU for your efforts.

Would you please email to me the cover page of each of the aforementioned studies?

Thank you.

B

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Monday, February 6, 2017 9:04 AM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Cc:** Nguyen, Khue <Nguyen.Khue@epa.gov>
**Subject:** RE: TCVP

Hi Bruce,

I can send you a CD with MRID 48773401 saved on it. Please confirm your preferred mailing address and note that it will take approximately two weeks for you to receive this submission. If you have any questions or concerns, please feel free to contact me.

James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Friday, February 03, 2017 5:05 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

Can you create a compressed zip file? If not, can you send me a CD?

Bruce

Have a good weekend.

B

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Friday, February 3, 2017 3:46 PM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Subject:** RE: TCVP

Hi Bruce,

I was able to obtain an electronic copy of the submission, however this document is over 1000 pages long, there is no way that I can email you a file this size.

James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Friday, February 03, 2017 3:16 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

Yes, thank you…I saw that information in your response to Doug Spilker.

What I need are copies of those reports…any chance you could use some else's CPU?

Thanks again.

Bruce

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Friday, February 3, 2017 3:14 PM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Subject:** RE: TCVP

Hi Bruce,

An acute CCA study report was found embedded in the repeat CCA study report (MRID 48773401) which was discovered when we were working on the repeat CCA DER. That acute CCA study should have been submitted as a separate study, so that it would have been assigned a separate MRID#. However, since the acute study was submitted as part of the repeat report, it had to have the same MRID#. Therefore, the acute study was referred to as MRID 48773401a in the TCVP risk assessment. Unfortunately, I do not have access to MRID 48773401 (due to CPU issues), however both are contained in under the same MRID number.

I hope this information is helpful,

James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Friday, February 03, 2017 3:00 PM

**To:** Parker, James <Parker.James@epa.gov>
**Subject:** TCVP
**Importance:** High

James,

Would you  please send me copies of the submissions (MRID 48773401 and 48773401a)?

# Thank you ever so much!!!

Bruce

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/6/2017 3:06:22 PM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: TCVP
**Attachments**: 487734-00-XX.pdf

Hi Bruce,

The transmittal sheet associated with MRID #48773401 is attached above. If you'd still like for me to mail you the associated CD, please send me your mailing address.

Best Regards,
James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Monday, February 06, 2017 9:15 AM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

James,

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**Cc:** Nguyen, Khue <Nguyen.Khue@epa.gov>
**Subject:** RE: TCVP

Hi Bruce,

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James P.

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Hi Bruce,

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James P.

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James P.

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**Sent:** Friday, February 03, 2017 3:00 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** TCVP
**Importance:** High

James,

Would you  please send me copies of the submissions (MRID 48773401 and 48773401a)?

# Thank you ever so much!!!

Bruce

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/3/2017 8:17:04 PM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: TCVP

Will try…

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Friday, February 03, 2017 3:16 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP

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Bruce

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**Subject:** RE: TCVP

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**To:** Parker, James <Parker.James@epa.gov>
**Subject:** TCVP
**Importance:** High

James,

Would you please send me copies of the submissions (MRID 48773401 and 48773401a)?

Thank you ever so much!!!

Bruce

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 1/26/2017 6:45:15 PM
**To**: Doug Spilker [doug.spilker@bayer.com]
**Subject**: RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment (MRID 48773401 vs. 48773401a?

Hi Doug,

An acute CCA study report was found embedded in the repeat CCA study report (MRID 48773401) which was discovered when we were working on the repeat CCA DER. That acute CCA study should have been submitted as a separate study, so that it would have been assigned a separate MRID#. However, since the acute study was submitted as part of the repeat report, it had to have the same MRID#. The acute study was assigned MRID 48773401a.

I hope this information is helpful,

James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

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**From:** Doug Spilker [mailto:doug.spilker@bayer.com]
**Sent:** Thursday, January 26, 2017 9:56 AM
**To:** Parker, James <Parker.James@epa.gov>
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**48773401a** ( see attached from HHRA). According to our consultant, Bruce Bernard, he made several additional submissions to the CCA study, but is unable to cross-reference them with this MRID number or any of his paperwork. Furthermore, it does not show up in NPIRS.

Could you please see what you can find out about this document (48773401a) – e.g. title, study number, etc. - and whether a specific DER is available?

Thanks for your help.

Best regards,

Doug

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Manager, EPA Regulatory Affairs

Bayer: Science For A Better Life

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Animal Health R&D, Regulatory Affairs
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Parker.james@epa.gov

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**Sent**: 1/26/2017 4:11:56 PM
**To**: Doug Spilker [doug.spilker@bayer.com]
**Subject**: RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment (MRID 48773401 vs. 48773401a?

Hi Doug,

I do not have any record of MRID 48773401a, hence I've contacted the science team and asked them for clarification. I will update you once I have additional information.

Best Regards,
James P.

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**Sent**: 12/29/2016 6:06:24 PM
**BCC**: Bruce Bernard [bernard@sra-intl.com]; smcnear@hartz.com; Doug Spilker [doug.spilker@bayer.com]
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**Sent**: 12/21/2016 8:22:10 PM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: TCVP Aerobic Soil Metabolism

Thank you and wishing you and your family a wonderful holiday…

James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Wednesday, December 21, 2016 2:19 PM
**To:** Parker, James <Parker.James@epa.gov>
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Thank you, James.

Best of the holidays to you and your family.

Bruce

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**Subject:** RE: TCVP Aerobic Soil Metabolism

Hi Bruce,

Attached are the PDF files for EPA's DER cover memo and DER amendment for a TCVP aerobic soil metabolism study MRID 48879901 (PC code 083702, DP Barcode 436212). The study classification remains ***Supplemental, can be used for risk assessments***.

Please let me know if you have any questions or issues with the files.

Best Regards,
James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Tuesday, December 13, 2016 7:39 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** RE: TCVP Aerobic Soil Metabolism

Thank you, James.

---

**From:** Parker, James [mailto:Parker.James@epa.gov]
**Sent:** Tuesday, December 13, 2016 3:27 PM
**To:** Bruce Bernard <bernard@sra-intl.com>
**Subject:** RE: TCVP Aerobic Soil Metabolism

Hi Bruce,

Based on our current schedule, I anticipate issuing the DER response document to you by Friday, December 23rd.

Regards,
James P.

---

**From:** Parker, James
**Sent:** Tuesday, December 13, 2016 2:38 PM
**To:** 'Bruce Bernard' <bernard@sra-intl.com>
**Subject:** RE: TCVP Aerobic Soil Metabolism

Hi Bruce,

I've contacted the science team and will provide you with an update as soon as it is available.

Best Regards,
James P.

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Tuesday, December 13, 2016 1:24 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** FW: TCVP Aerobic Soil Metabolism
**Importance:** High

Dear James,

Would you please give me an update on the material I sent to you back in October (see below)?

Thank you.

Bruce Bernard

---

**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Monday, October 10, 2016 9:24 AM
**To:** James Parker (parker.james@epa.gov) <parker.james@epa.gov>
**Subject:** TCVP Aerobic Soil Metabolism
**Importance:** High

Dear James,

Attached please find the TCVP Task Force responses to EPA's comments on the above identified study.

Thank you for handling this matter.

Sincerely,

Bruce Bernard

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 12/21/2016 2:07:14 PM
**To**: Bruce Bernard [bernard@sra-intl.com]
**Subject**: RE: TCVP Aerobic Soil Metabolism
**Attachments**: 083702_48879901_DER-Fate_835.4100_12-19-16.pdf; 083702_436212_DER-Memo_12-19-16.pdf

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**Subject:** RE: TCVP Aerobic Soil Metabolism

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**Subject:** FW: TCVP Aerobic Soil Metabolism
**Importance:** High

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Bruce Bernard

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**From:** Bruce Bernard [mailto:bernard@sra-intl.com]
**Sent:** Monday, October 10, 2016 9:24 AM
**To:** James Parker (parker.james@epa.gov) <parker.james@epa.gov>
**Subject:** TCVP Aerobic Soil Metabolism
**Importance:** High

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Bruce Bernard

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 8/3/2016 4:30:58 PM
**To**: Doug Spilker [doug.spilker@bayer.com]
**Subject**: RE: TCVP Question

Hi Doug,

Unfortunately, I was out of the office last week and some of this week. The next phase of the tetrachlorvinphos (TCVP) registration review process will be the publication of the Proposed Interim Decision, Revised Risk Assessments and Response to Public Comments, which are scheduled to post to the TCVP docket in December 2016. In reference to your information request, Bayer should submit a FOIA request to www.epa.gov/foia, and select "Make a new request". Please let me know if you have any issues submitting this request utilizing the FOIA process.

Best Regards,
James P.

James Parker, M.S.
Chemical Review Manager
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA
Phone: 703-306-0469
Parker.james@epa.gov

NOTICE: This communication may contain privileged or other confidential information. If you are not the intended recipient, or believe you have received this communication in error, please delete the copy you received, and do not print, copy, retransmit, disseminate, or otherwise use the information. Thank you.

**From:** Doug Spilker [mailto:doug.spilker@bayer.com]
**Sent:** Wednesday, July 27, 2016 2:42 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** FW: TCVP Question

Hi James,
Any update on this? Also, what is the next step in this process? Is it the Agency's Interim Decision document or what? Is there a date in your system for completion?

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

---

**From:** Doug Spilker
**Sent:** Friday, July 22, 2016 4:59 PM
**To:** Parker, James
**Subject:** Re: TCVP Question

Hi James, Primarily the correspondence. I have the notices and risk assessments etc.
what I am missing are documents of submissions, data matrices, any agreements, MRID responses, etc.
Shall we talk about?
Doug
Douglas A. Spilker, Ph. D.
Bayer Animal Health
This message may be brief since it was sent from my iPhone (816-506-3102). Office #913-268-2751.

On Jul 22, 2016, at 3:05 PM, Parker, James <Parker.James@epa.gov> wrote:

> Hi Doug,
>
> There has been an extensive working relationship between the Agency and SRA Internation since before the RED. What type of information are you looking for: regulatory documents (i.e., notices and decisions), science documents (i.e., risk assessments and DERs), correspondence (i.e., emails and submissions)?
>
> James P.
>
> ---
>
> **From:** Doug Spilker [mailto:doug.spilker@bayer.com]
> **Sent:** Friday, July 22, 2016 3:40 PM
> **To:** Parker, James <Parker.James@epa.gov>
> **Subject:** TCVP Question
>
> Hi James,
>
> Hope you are staying cool! It is so hot in KC, it was 80F at 6am this morning.
>
> As you are likely aware, we inherited the TCVP Task Force arrangement with Hartz and SRA International (Bruce Bernard). It has worked okay, but the arrangement is a little awkward with SRA International; we at Bayer commonly work directly with EPA and not through a consultant, since we have our own regulatory group. I have never felt like I was always getting copies of all the

correspondence to/from the Agency. You have done very good lately, but I don't really have a historical file that goes back very far. We did not get much from KMG when we bought their products.

Now my question: How thick is the Regulatory "Jacket" containing all of the PRED correspondence for TCVP? Might it be something that I could request a copy of, by paying a per page charge? If it is too thick, then maybe I consider just since the last DCI, or other suggestion by you.

Your thoughts would be appreciated.

Best Regards,

Doug

Douglas A. Spilker, Ph.D.
Manager - EPA Reg. Affairs

Bayer Animal Health
Bayer HealthCare LLC
P.O. Box 390
Shawnee Mission, KS 66201-0390
USA

Office: +1 -913-268-2751
Mobile: +1 -816-506-3102
Email: doug.spilker@bayer.com

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*The information contained in this e-mail is for the exclusive use of the intended recipient(s) and may be confidential, proprietary, and/or legally privileged. Inadvertent disclosure of this message does not constitute a waiver of any privilege. If you receive this message in error, please do not directly or indirectly use, print, copy, forward, or disclose any part of this message. Please also delete this e-mail and all copies and notify the sender. Thank you.*

Message

**From**: Lowit, Anna [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1D3428A2C0B84D5099124A0460BABD53-ANNA B. LOWIT]
**Sent**: 10/19/2016 7:31:05 PM
**To**: Yuki.SAKURATANI@oecd.org
**CC**: Reaves, Elissa [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=031646294ce14535ae428ab2f8d388c4-Reaves, Elissa]
**Subject**: RE: [Reminder] OECD IATA Case Studies Project - Review results -
**Attachments**: Response Form (Case Study 2016-2) USEPA Pesticides.pdf; Response Form (Case Study 2016-2) USEPA Pesticides.docx; Revised OECD IATA Case Study 2016_OP CRA.docx; Revised OECD IATA Case Study 2016_OP CRA.pdf; Additional Comment on Case Study 2 (NL)_responses.docx; Additional Comment on Case Study 2 (DE)_response.docx

Hi Yuki

Sorry for the tardiness on this.

Anna

*Anna B. Lowit, Ph.D.*
Senior Science Advisor
Immediate Office
Office of Pesticide Programs, USEPA
w: 703-308-4135
c: 703-258-4209

---

**From:** Yuki.SAKURATANI@oecd.org [mailto:Yuki.SAKURATANI@oecd.org]
**Sent:** Tuesday, October 11, 2016 9:28 AM
**To:** Lowit, Anna <Lowit.Anna@epa.gov>
**Cc:** Reaves, Elissa <Reaves.Elissa@epa.gov>
**Subject:** RE: [Reminder] OECD IATA Case Studies Project - Review results -

Dear Anna,

Could you please let me know about when you can provide revised case study?

Best regards,

Yuki

---

**From:** SAKURATANI Yuki, ENV/EHS
**Sent:** 16 September, 2016 6:06 PM
**To:** 'Lowit, Anna'; Reaves, Elissa
**Subject:** RE: [Reminder] OECD IATA Case Studies Project - Review results -

Dear Anna,

Thank you for letting me know your situation.
This is no problem.

Best regards,

Yuki

---

**From:** Lowit, Anna [mailto:Lowit.Anna@epa.gov]
**Sent:** 16 September, 2016 5:10 PM
**To:** SAKURATANI Yuki, ENV/EHS; Reaves, Elissa
**Subject:** RE: [Reminder] OECD IATA Case Studies Project - Review results -

Hey Yuki

I don't think we will make your 19th date. Can we have a few extra days?

Anna

*Anna B. Lowit, Ph.D.*
Senior Science Advisor
Immediate Office
Office of Pesticide Programs, USEPA
w: 703-308-4135
c: 703-258-4209

---

**From:** Yuki.SAKURATANI@oecd.org [mailto:Yuki.SAKURATANI@oecd.org]
**Sent:** Tuesday, September 06, 2016 8:24 AM
**To:** karin.aschberger@ec.europa.eu; tara.bartonmaclaren@hc-sc.gc.ca; Benson, Amy <Benson.Amy@epa.gov>; stephanie.bopp@ec.europa.eu; jorgen.henriksson@kemi.se; hirose@nihs.go.jp; mlh@mst.dk; hmikim@korea.kr; tatiana.netzeva@echa.europa.eu; Maila.PUOLAMAA@ec.europa.eu; mike.rasenberg@echa.europa.eu; JCRowlands@dow.com; sneha.satya@nicnas.gov.au; ksullivan@pcrm.org; jay_west@americanchemistry.com; lidka.maslankiewicz@rivm.nl
**Cc:** Tanja.Burgdorf@bfr.bund.de; sunhwachung@korea.kr; genevieve.deviller@solvay.com; matthew.gagne@hc-sc.gc.ca; miriam.jacobs@phe.gov.uk; iprecious@korea.kr; sunil.kulkarni@hc-sc.gc.ca; kwontox@korea.kr; Lowit, Anna <Lowit.Anna@epa.gov>; Reaves, Elissa <Reaves.Elissa@epa.gov>; andrea.richarz@ec.europa.eu; leida.rijnhout@eeb.org; t-yamada@nihs.go.jp; Eeva.LEINALA@oecd.org
**Subject:** [Reminder] OECD IATA Case Studies Project - Review results -

Dear Members of the IATA Case Studies Project,

This is a gentle reminder.
Please note that the deadline for the comments on discussion points at the November meeting and the submission of revised case study is **September 19th** (see the following mail).

Best regards,

Yuki

---

**From:** SAKURATANI Yuki, ENV/EHS
**Sent:** 19 July, 2016 1:17 PM
**To:** ASCHBERGER Karin; BARTONMACLAREN Tara s; BENSON Amy; BOPP Stephanie; HENRIKSSON Jorgen; HIROSE Akihiko; HOLMER Marie louise; KIM Hyunmi; NETZEVA Tatiana; PUOLAMAA Maila; RASENBERG Mike; ROWLANDS J craig; SATYA Sneha; SULLIVAN Kristie; WEST Jay; WIJKHUIZEN MASLANKIEWICZ Lidka
**Cc:** BURGDORF Tanja; CHUNG Sun hwa; DEVILLER Genevieve; GAGNE Matthew; JACOBS Miriam; KIM Pyeong soon; KULKARNI Sunil; KWON Jungtaek; LOWIT Anna; REAVES Elissa; RICHARZ Andrea; RIJNHOUT Leida; YAMADA Takashi; LEINALA Eeva, ENV/EHS
**Subject:** OECD IATA Case Studies Project - Review results -

Dear Members of the IATA Case Studies Project,

Thank you very much for your valuable comments on the case studies submitted to the IATA Case Studies Project.
We have posted compiled comments for each case study and original files submitted by reviewers on the clear space site for the project.
https://community.oecd.org/community/iatacasestudies
Please look over the reviewer's comments and consider what you think are the key overall points/themes for discussion to focus on at the November meeting and how the considerations developed last year could be elaborated by adding this experience.
Please send the secretariat your input **by September 19th.**

To lead countries:
Please prepare the responses to the review's comments by using the form assigned to each case study on the clear space and send it to us by **September 19th** with a revised case study, if you revise it.

Best regards,

Yuki

OECD
BETTER POLICIES FOR BETTER LIVES

**Yuki Sakuratani**
Administrator, QSAR and Hazard Assessment
Environment Directorate, Environment, Health and Safety Division

2, rue André Pascal - 75775 Paris Cedex 16
Yuki.SAKURATANI@oecd.org || www.oecd.org/chemicalsafety
Tel: +33 1 45-24-98-19

Message

**From**: RAB57 - HED/OPP [no-reply@sharepointonline.com]
**Sent**: 10/11/2016 6:28:02 PM
**To**: Taylor, Linda [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=cbfa6aa22daf4af8ba2e13991525a046-Linda Taylor]
**Subject**: RAB57 Peer Review - TCVP revised RA has been assigned to you

RAB57 - HED/OPP

# ***TCVP revised RA*** has been assigned to you

Modify my alert settings | View TCVP revised RA | View RAB57 Peer Review | Mobile View

| | |
|---|---|
| **Title:** | TCVP revised RA |
| **Predecessors:** | |
| **Priority:** | (2) Normal |
| **Task Status:** | Not Started |
| **% Complete:** | 0% |
| **Document Created By:** | Drew, Danette |
| **Assigned To:** | Britton, Wade; Taylor, Linda; Metzger, Michael; Habiba, Uma; Lowe, Kelly |
| **Description:** | Master document for Team inputs |
| **Start Date:** | 10/11/2016 |
| **Due Date:** | 10/21/2016 |
| **Completed:** | No |
| **Peer Review Type:** | Risk Assessment Documents for Branch QA-QC |

Last Modified 10/11/2016 2:27 PM by Drew, Danette

## I. Introduction

The Natural Resources Defense Council (NRDC) submits these comments on the Environmental Protection Agency's (EPA's) Tetrachlorvinphos Human Health Draft Risk Assessment for Registration Review (Dec. 21, 2015). We appreciate EPA's reassessment of the health risk associated with tetrachlorvinphos (TCVP)-containing flea and tick products and the additional analyses conducted since the November 6, 2014 Response to our Petition to Cancel all Pet Uses of Tetrachlorvinphos. Some of the findings in this draft risk assessment (DRA) are in accordance with the material we presented in our original petition in 2009, where we concluded that the available science on the danger of organophosphate (OP) pesticides, including TCVP, and the levels of exposure resulting from use in pet products pose an unacceptable level of risk to children. We urge EPA to fill the remaining gaps in this assessment and initiate proceedings to cancel all pet uses for TCVP.

TCVP, also known as Rabon™ and Gardona™, is a pesticide used to control fleas and ticks on household pets, as well as livestock. It belongs to a class of pesticides called organophosphates, which are highly toxic to the nervous system of both invertebrates (fleas and ticks) and mammals (people and pets). TCVP pet products are one of the only remaining uses of these dangerous chemicals inside the home.[1]

Although this DRA improves upon the November 6, 2014 Residential Exposure Assessment, it continues to underestimate risks to children from TCVP-containing pet products by, among other things, utilizing unsubstantiated algorithms and assumptions, and failing to consider dermal exposure, which in previous assessments was found to contribute substantially to a child's risk.

## II. EPA Must Account for the Increased Vulnerability of Children

(A) The 10X FQPA uncertainty factor must be retained in the Final Risk Assessment.

In 2015, EPA conducted a literature review of the studies showing neurodevelopmental impacts from organophosphates. *See generally* OP Literature Review 2015.[2] The results of this literature review are summarized in section 4.4 of the DRA and conclude that the studies find evidence of impaired mental and psychomotor development, attentional problems, autism spectrum disorder, intelligence decrements, and ADHD.[3] These impacts occurred even without AChE inhibition, and neurodevelopmental impacts from

---

[1] And it is the only organophosphate product to which a child would have regular exposure. The other remaining in-home use is of another organophosphate, dichlorvos, in a pet strip only to be used in unoccupied areas. *See* Hot Shot Products & Solutions, http://www.hotshot.com/products-and-solutions/all-products/no-pest-strip.aspx.

[2] EPA Office of Pesticide Programs, Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, D331251 (Sept. 15, 2015), *available at* http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0440-0039.

[3] US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 25 and 26.

organophosphates have been shown in four cohorts across twelve studies.[4] These impacts are in addition to those reflected in EPA's similar findings for chlorpyrifos specifically.[5] EPA found that, together, all this evidence strongly supports the conclusion that prenatal exposures to organophosphates results in adverse neurodevelopmental effects in children. The OP Literature Review and the chlorpyrifos RHHRA firmly establish through extensive and careful analysis that prenatal organophosphate exposures cause adverse neurodevelopmental impacts.

The OP Literature Review and the DRA also accurately conclude that the neurodevelopmental effects are the most sensitive endpoint related to organophosphate toxicity. This is important because EPA policy requires selection of the most sensitive endpoint for quantitative evaluation in risk assessments in order to ensure adequate health protections for people. If the Agency protects against the most sensitive effects, it will also protect against any other effects that occur at higher levels of exposure.[6]

In the DRA, EPA appropriately applied the 10X safety factor for TCVP due to neurodevelopmental impacts.[7] EPA found that, "[g]iven the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor."[8] Likewise, because studies showed "neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children," EPA retained the 10x safety factor for "the population subgroups that include infants, children, youths, and women of childbearing age." [9] These conclusions are correct; any deviation from the 10X safety factor in the final risk assessment would violate FIFRA, which mandates that the 10X safety factor "*shall* be applied," and permits EPA to use a different margin of safety "*only if*, on the basis of reliable data, such margin *will be safe* for infants and children." 21 U.S.C. § 346a(b)(2)(C)(ii) (emphasis added).

(B) EPA's continued use of 10% cholinesterase inhibition as the critical health endpoint in the DRA is contrary to the scientific evidence finding neurodevelopmental effects at lower doses.

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[4] US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 26.

[5] *See* Chlorpyrifos RHHRA at 26-49.

[6] EPA OPP, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment at 8 (2002). *See, e.g.*, http://www.epa.gov/pesticides/reregistration/atrazine/atrazine_update.htm, —Reproductive effects are the most sensitive effects observed in atrazine toxicity tests and, as such, our efforts to regulate the pesticide to protect against these effects through drinking water exposure will protect against all other effects that occur at higher levels.‖

[7] US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 27.

[8] US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 27.

[9] US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 27.



ED_002155A_00018784-00002

In order to ensure that people are protected from adverse health impacts, it is EPA's policy to use the most sensitive endpoint to calculate regulatory limits for risk assessment.[10] In the OP Literature Review, EPA finds that the neurodevelopmental effects are the most sensitive endpoint because they occur at exposures too low to cause 10% cholinesterase inhibition. Inexplicably, EPA nevertheless continues to use 10% cholinesterase inhibition as its risk assessment endpoint. By not using the most sensitive endpoint (neurodevelopmental effects) to set regulatory limits, EPA is acting contrary to its findings and the evidence and falls far short of its obligation to protect children from prenatal toxicity. *See* 21 U.S.C. § 346a(b)(2)(C)(ii)(I) (requiring agency to "*ensure* that there is a reasonable certainty that *no harm will result* to infants and children from aggregate exposure to the pesticide chemical residue") (emphasis added). Continuing to regulate to 10% cholinesterase inhibition is contrary to the law and science.[11]

## III. EPA Must Evaluate and Include Dermal Exposure from Pet Uses of TCVP in Accordance with Previous Evaluations of Dermal Toxicity

(A) EPA cannot support the reversal from previous assessments about dermal hazards from TCVP.

EPA's Occupational and Residential Exposure (ORE) Assessment, at p18, describes the updates completed since the 2014 assessment as including "the determination of no dermal hazard from TCVP." Similarly, in the DRA, at p45, the determination that there is no non-cancer dermal hazard for TCVP is listed as a change from the previous assessment. However, neither document includes a description, or citation, to new evidence discussing the dermal toxicity of TCVP. The dermal study that was relied upon to make the determination of no dermal hazard is described only in Table A.2.2 DRA, at p70, where the citation, MRID 41342001 (1989), reveals that it is the same study relied upon in previous assessments as evidence *for* dermal toxicity of TCVP. In particular, the 2008 Human Health Assessment Scoping Document in Support of Registration Review included a summary of the available studies upon which hazard identification could be determined. This review concluded, at p4, "Although there were deficiencies in the available 21-day dermal study, the study did demonstrate that cholinesterase inhibition to be the principal toxicological effect of concern via the dermal route." As a result of this review, in 2008, EPA did not request any additional studies related to the assessment of toxicity via the dermal route from the registrant nor identify studies in the published literature that should be considered as part of the registration review.

The two previous risk assessments EPA performed for TCVP in 2002 and 2014—both of which were conducted *subsequent* to the dermal study (MRID 41342001 (1989))—included assessment of exposure via the dermal route. In the 2014 assessment, the estimated dermal dose for children from pet uses far exceeded other routes of exposure and was close to the level of concern (LOC) utilized in that assessment and below the LOC EPA determined in the DRA of 1,000.[12] The DRA does not provide *any* explanation

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[10] EPA OPP, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment at 8 (2002).

[11] See also Farmworker and Conservation Chlorpyrifos RHHRA Comments at 23-28 (Apr. 30, 2015)

[12] The dermal MOEs for flea collars in the 2014 assessment ranged from 370 to 980 for children. At the low end this is close to the Level of Concern used in the 2014 assessment of 100 and all of these MOEs are below the level of concern used in the 2015 DRA.



ED_002155A_00018784-00003

or rationale for this change in the evaluation of the dermal hazard—much less "good reasons" and a "detailed justification" for the reversal, *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009)—nor does it provide a description of evidence that differed from that considered in previous risk assessments. Accordingly, EPA must include and evaluate the dermal hazard in its final risk assessment.

(B) EPA's determination that there is no dermal hazard from TCVP is not substantiated by the evidence.

EPA's prior conclusion that the 21 day Dermal Toxicity Study (MRID 41342001) demonstrated the toxic effect of cholinesterase inhibition via the dermal route is supported by the finding of cholinesterase inhibition in plasma. This pattern is observed in both male and female rats at the mid and high dose levels, although the decrease was only statistically significant at the high dose level. Given the low statistical power as a result of the small sample size, the dose response trend in the females of 32% reduction at the mid-dose level and 67% at the high dose level should not be discarded.[13] In addition, both of these values exceed the 10% for cholinesterase inhibition that EPA considers to be biologically significant.[14] Therefore, consistent with the determination made in the 2008 Scoping Document, this study does provide evidence for cholinesterase inhibition as a result of dermal exposure.

In addition, the epidemiologic literature suggests that toxic, neurodevelopmental effects can occur at levels below what would be expected to result in detectable cholinesterase inhibition in brain and RBC. EPA's review of the evidence on the impacts of OP pesticides concluded that there is considerable uncertainty as to whether the 10% cholinesterase inhibition provides sufficient protection for neurodevelopmental impacts to the developing fetus.[15] Therefore, the lack of 10% cholinesterase inhibition finding in red blood cells or the brain in the 21-day dermal toxicity study is not sufficient evidence to support a finding of no dermal hazard for TCVP.

Lastly, limitations in the Dermal Toxicity Study reduce its capacity to detect cholinesterase inhibition and likely underestimate the true impact via the dermal route. As noted in the 2008 Human Health Assessment Scoping Document, the dermal study EPA relied upon for the determination that there is no dermal hazard from TCVP has "deficiencies." These deficiencies include a very small sample size that was further reduced as a result clinical problems resulting in blood samples being discarded. As a result, only 3 animals were evaluated in one of the treatment groups giving this study very low statistical power detect a decrease in cholinesterase.[16] Additionally, the study failed to follow the standard protocol which requires that the test material be applied over "not less than 10 percent of the body surface area."[17] For the low- and mid-dose groups the test material was applied to a 10-fold lower area (1% of the body

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[13] DER MRID 41342001 (1989). 21-Day Dermal Study in Rats with Rabon Technical. p.23

[14] EPA 2006. Organophosphorus Cumulative Risk Assessment – 2006 Update

[15] EPA Office of Pesticide Programs, Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, D331251 (Sept. 15, 2015), *available at* http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0440-0039. And summarized in the US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 27

[16] DER MRID 41342001 (1989). 21-Day Dermal Study in Rats with Rabon Technical. Table 11 p.60

[17] OECD Test No. 410: Repeated Dose Dermal Toxicity: 21/28-day Study http://www.oecd-ilibrary.org/environment/test-no-410-repeated-dose-dermal-toxicity-21-28-day-study_9789264070745-en

surface area) resulting in a significant underestimation of the toxicological effects of dermal exposure. As a result of these deficiencies, the impact of dermal exposure to TCVP on cholinesterase inhibition is likely substantially greater than what was reported in this study.

EPA's failure to consider dermal exposure and toxicity in the DRA ignores the findings of the Dermal Toxicity Study and greatly underestimates the potential for harm to the developing brain of children from exposures to TCVP in pet products. Therefore, EPA must include and evaluate the dermal hazard in its final risk assessment.

## IV. EPA Must Utilize the Best Available Data to Evaluate Exposures from TCVP in Flea Collars

(A) The Davis Study has met the appropriate scientific and ethical criteria and should be relied upon for the evaluation of exposures from TCVP containing flea collars.

In the DRA, EPA considers the exposure calculations performed using residue levels measured in the Davis Study to be preliminary pending review of ethical considerations to be considered by the Human Subjects Review Board (HSRB). Since the DRA was posted to the docket, a meeting of the HSRB was held where the relevant questions regarding the Davis Study were discussed. In the minutes of this meeting it is reported that the Board unanimously approved the response concluding that the study "was sufficiently scientifically sound to be used appropriately by EPA."[18] In response to the two ethics review questions, the Board unanimously concluded that there were not ethical concerns that "would prevent the EPA from using the pet transferable residue data derived from the study for making a decision to impose a more stringent regulatory decision than could be justified without the data."[19]

Based on the conclusions of the HSRB there are no scientific or ethical reasons why EPA should not rely on the residue data reported in the Davis Study. As a result, the exposure calculations performed based on this data should be finalized.

(B) EPA's utilization of transferable residue data from the amitraz study is not supported by the evidence and should not be relied upon to evaluate risk.

In the DRA, EPA expresses uncertainty about what data should be utilized as the basis for determining the fraction of residue available for transfer ($F_{AR}$) as part of the evaluation of children's residential post-application exposures resulting from flea collars with TCVP. As a result, the risk calculations are performed using results from the Davis Study and from the amitraz pet collar residue transfer study. EPA's rationale for using the amitraz study was that the $F_{AR}$ value (0.14%) were greater than what was reported in the propoxur pet collar residue transfer study (0.072%), which was used in the 2014 assessment. However, EPA provides no evidence that this value is appropriate for evaluating exposures from TCVP pet collars. The three different pet collar residue transfer studies cited by EPA in the 2015

[18] Draft Minutes of the United States Environmental Protection Agency (EPA) Human Studies Review Board (HSRB) January 12–13, 2016, Public Meeting Docket Number: EPA–HQ–ORD–2015–0588 p.27

[19] Draft Minutes of the United States Environmental Protection Agency (EPA) Human Studies Review Board (HSRB) January 12–13, 2016, Public Meeting Docket Number: EPA–HQ–ORD–2015–0588 p.28

and 2014 assessments have all differed substantially from each other – amitraz (0.14%), propoxur (0.072%) and deltamethrin (0.003%). There is no information provided in the DRA that provides evidence that the TCVP residues would be similar to the amitraz collar. Relatedly, EPA provides insufficient evidence that the amitraz study serves as a better surrogate than the default value of 2%, as EPA's Standard Operating Procedures otherwise would require in the absence of a TCVP-specific study.

A comparison of the three flea collars with different active ingredients indicates that there is considerable variability between the collars. Further support for the large variation in transferable residue from flea collars comes from the Davis study. There, the scientists concluded that "the overall magnitude of transferable residues from the TCVP collars was much greater than was observed in [a] previous study with a [chlorpyrifos]-containing flea collar."[20] Among other things, this "45-fold" "difference in magnitude," the study suggested, could be "attributed to … different formulation matrices between the two types of collars leading to greater release of TCVP."[21] EPA has not provided evidence that this variability has been appropriately considered. Therefore, the risk calculations based on exposure assessments conducted using the amitraz pet collar residue transfer study cannot be used to assess risks from TCVP pet collars.

## V. EPA Must Not Rely on Unsubstantiated Assumptions and Algorithms to Calculate Exposures

(A) EPA's assumption that flea collars "are designed to release the active ingredient in liquid form" is not substantiated by the evidence and should not be relied upon to evaluate risk.

In the DRA, the exposure calculations for flea collars are performed using the values recommended in the Standard Operating Procedure (SOP) for both liquid and solid formulations. However, in all of the documents in the docket for the registration review, the only evidence describing the collar formulation supports the characterization as a solid formulation. EPA summarizes this evidence in the document containing responses to the arguments raised in the NRDC's opening brief. In this document, EPA confirmed that more than half of the total pet collar products include text on the label describing the release of a powder from the collar. EPA then concludes that "some collars may act by extrusion of the active ingredient from the collar matrix as fine dust." [22]

In contrast, EPA's only justification for the characterization of the collars as liquid formulations is a reference to the 2012 SOP and the explanation that this position was based upon "research conducted at the time of the SOP development." No citation or evidence is provided that any of the TCVP collars, currently available on the market, function in any manner that resembles a liquid. Therefore, EPA must

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[20] Davis, M. Keith, et al. "Assessing intermittent pesticide exposure from flea control collars containing the organophosphorus insecticide tetrachlorvinphos." *Journal of Exposure Science and Environmental Epidemiology* 1-7 (2008): 5-6.

[21] Davis, M. Keith, et al. "Assessing intermittent pesticide exposure from flea control collars containing the organophosphorus insecticide tetrachlorvinphos." *Journal of Exposure Science and Environmental Epidemiology* 1-7 (2008): 6.

[22] EPA 2015. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council Inc's (NRDC) August 5, 2015 Opening Brief in *NRDC v EPA,* Case No. 15-7005 (9th Cir.) p.8



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not evaluate the risk to children from these products based on exposure calculations which rely on the unsubstantiated assumption that the collars are formulated as a liquid.

In the DRA, EPA indicated that they have sought clarification from the registrants whether the collars are "designed" to release TCVP in liquid or solid form.[23] The appropriate inquiry should be the form in which the collars *actually* release TCVP; not merely the form in which they are *designed* to release the pesticide. But because EPA has not made any of those responses public, NRDC is not able at this time to evaluate or respond to any representations of the manufacturers.

(B) EPA's exposure calculation using the assumption that the collar is formulated as a liquid underestimates the exposures actually documented in the Davis study.

The Davis Study was designed to evaluate exposure to TCVP that could occur from the use of a TCVP-containing collar on a pet dog.[24] Therefore, any exposure calculation which results in a daily exposure that is less than was measured in the Davis Study greatly underestimates exposure and cannot be relied upon to evaluate risk. EPA must not evaluate risk based on exposure assessments that result in less exposure than was measured in this Davis Study. However, when EPA's algorithm is applied to the assumption that the collar is formulated as a liquid, it underestimates the exposure measured in the Davis Study.

To compare the exposure level calculated by EPA based on the unsubstantiated algorithm and assumptions, we looked at the exposures EPA estimated for a flea collar (registration #2596-62 for a large dog) with a quantity of active ingredient (4,670 mg) similar to what was reported as used in the Davis Study (4,800 mg). For this collar, using EPA methods, and the assumption that the collar is formulated as a liquid, you would calculate that 6.8 mg of TCVP would get on the skin of an adult per day[25] and that 0.3 mg would be on two hands.[26] In the Davis Study, the peak level of residue measured on <u>one</u> hand after 5 minutes of petting a dog over the collar was 24 mg of TCVP in study 1. In study 2, the mean residue measured on <u>one</u> hand after 5 minutes of petting was 19 mg on the neck over the collar and 8 mg on the neck with the collar removed.

This comparison reveals that EPA's calculations—when they include a liquid assumption—greatly underestimated the exposure, which was measured directly in the Davis Study. Accordingly, even if EPA concludes that TCVP pet collars release a liquid, EPA should

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[23] US EPA Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review p. 48.

[24] Davis, M. Keith, et al. "Assessing intermittent pesticide exposure from flea control collars containing the organophosphorus insecticide tetrachlorvinphos." *Journal of Exposure Science and Environmental Epidemiology* 1-7 (2008): 2

[25] Exposure (E) on the skin (mg/day) is equal to the transfer coefficient (TC) * transferable residue (TR) * exposure time (ET) where TC for an adult (liquid scenario) is 5,200 cm2/hr, ET is 0.77 hrs, and TR = (Application rate (or AI in the collar) * $F_{AR}$)/Surface Area of the pet (SA). EPA calculated a $F_{AR}$ based on the Davis Study of 0.004. Therefore for this collar, the TR is 4,670 mg*0.004/11,000 and E= 5,200 * 0.001698*0.77.

[26] The quantity on the hands is E*Fraction of ai on hands ($F_{ai\ hands}$). $F_{ai\ hands}$ for a liquid is assumed to be 0.04.



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reconsider the validity of the algorithms and assumptions used to calculate post-application residential exposure to TCVP residues from pet collars. When there is a peer-reviewed, scientifically valid study that is designed to document exposure, EPA must account for the results in the exposure assessment even if they contradict the complex formulas based on uncertain assumptions.

## VI. EPA Must Evaluate Real-World Scenarios for Children's Exposure to Pet Uses of TCVP

(A) EPA fails to protect children who spend more than 1 hour per day in contact with their pet.

EPA has utilized data from a single study, with only nine children, as the basis for its Exposure Time (ET) variable derivation such that the risk assessment is based on the assumption that toddlers spend only one hour per day playing with their pets. Because EPA chose to use the median of this extremely limited study, half of the children spent more than one hour per day playing with their pets and are therefore not protected by EPA's standard. Importantly, at least two of the nine children in the study spent more than an hour and a half with their pets each day, and at least one spent over two hours. In the Davis Study, the researchers noted that two t-shirts worn by kids in study 2 were found to have significantly higher levels of TCVP residue. The authors concluded that these higher levels were the result of increases in the amount of time those children spent in direct contact with their pet dogs on those days.[27] This finding is additional evidence that some children spend greater amounts of time with a pet treated with TCVP and as a result will likely experience greater exposure to TCVP.

EPA does not provide evidence from studies of children's interactions with their pets to support the claim that the assumptions in the SOP – that one hour of exposure to the treated pet during which a child touches the pet 4 times and engages is hand-to-mouth activity- reflects a "reasonable high end estimate of time spent in contact with a dog treated with TCVP pet products".[28] Furthermore, EPA's repeated insistence that the SOP captures "vigorous" contact with a pet and that a child would not be expected to have this type of contact with a pet for more than 1 hour per day is not supported by any evidence. Lastly, EPA's argument that utilizing the 90th percentile would result in "exposure estimates that are overly conservative and unrealistic; particularly given the already health protective nature of the assessment methods and inputs"[29] is contrary to the evidence – particularly EPA's decision to ignore dermal toxicity and indirect hand-to-mouth exposures, which both underestimate exposures. In order to protect all of these children and account for the limited nature of the dataset, EPA should use the upper portion of the distribution (90th -95th percentile) and assume that children spend at least two hours with their pets per

[27] Davis, M. Keith, et al. "Assessing intermittent pesticide exposure from flea control collars containing the organophosphorus insecticide tetrachlorvinphos." *Journal of Exposure Science and Environmental Epidemiology* 1-7 (2008): 6

[28] EPA 2015. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council Inc's (NRDC) August 5, 2015 Opening Brief in *NRDC v EPA,* Case No. 15-7005 (9th Cir.) p.9

[29] EPA 2015. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council Inc's (NRDC) August 5, 2015 Opening Brief in *NRDC v EPA,* Case No. 15-7005 (9th Cir.) p.10



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day. Indeed, in other risk assessments, EPA has assumed that children spend two hours per day playing with their pets.[30]

(B) EPA ignores indirect exposure routes that could contribute to a child's total exposure to TCVP.

In the DRA, EPA failed to evaluate indirect exposure routes, such as contact with a surface contaminated by pesticide residue or mouthing of objects which contain pesticide residue. There is evidence in the published literature that TCVP residues can contaminate surfaces that children can come into contact with and that children's object-to-mouth activity can result in increased exposures to chemicals. In the Davis Study, the t-shirts worn by children playing with dogs wearing TCVP flea collars were found to have significant TCVP residues. The authors of the study concluded that these t-shirts, and other clothing, could be a potential source of exposure.[31] Other surfaces which could reasonably be expected to have TCVP residues include, furniture, rugs, pet bedding, and any other place in the home that comes into contact with the fur of the pet and that a child might touch with their hand or put in their mouth.

Published studies, such as Stephen Ko et al., *Relationship of video assessments of touching and mouthing behaviors during outdoor play in urban residential yards to parent perceptions of child behaviors and blood lead levels*, Journal of Exposure Science and Environmental Epidemiology 17, 47-57 (2007), demonstrate that object to mouth is significant route of exposure and found that, on average, the children in the study put objects in their mouth while playing 15 times per hour (and, at the high end, 66 times per hour).

EPA's argument that the indirect exposures would be at a lower level than direct hand-to-mouth exposure ignores the science behind evaluating the total aggregate exposure experienced by a child from all of the relevant exposure routes. Because it is reasonable to assume that a child could come into contact with TCVP residues by both direct *and* indirect methods in a single day, the total dose experienced by the child is the sum of all of the exposure pathways. EPA's rationale for not evaluating indirect hand-to-mouth exposures, as explained in the memo responding to NRDC's arguments, is that the "addition of object-to-mouth exposure would have little to no impact on the combined risks" and that "combining these scenarios with the dermal exposure scenario would be overly conservative because of the conservative nature of each individual assessment."[32] These arguments are contradictory, and neither is substantiated with evidence specific to exposures to TCVP residues from pet uses. EPA provides no documentation that a child's cumulative exposure to surfaces contaminated with residues resulting from contact with a treated dog or cat (i.e. the bed where the dog sleeps and/or the chair where the grooms themselves) would be so low as to not contribute to the cumulative daily exposure. And conversely, if the exposures levels

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[30] *See* EPA Reregistration Eligibility Decision for Dichlorvos (DDVP) 167 (July 31, 2006).

[31] Davis, M. Keith, et al. "Assessing intermittent pesticide exposure from flea control collars containing the organophosphorus insecticide tetrachlorvinphos." *Journal of Exposure Science and Environmental Epidemiology* 1-7 (2008): 6

[32] EPA 2015. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council Inc's (NRDC) August 5, 2015 Opening Brief in *NRDC v EPA,* Case No. 15-7005 (9th Cir.) p.12



ED_002155A_00018784-00009

are as low as EPA claims then it would not be overly conservative to include them. Lastly, EPA's claim that the other exposures scenarios are conservative and therefore inclusive of this exposure is not substantiated – EPA's decision to ignore the evidence of dermal toxicity and to assume that the median exposure duration is protective are not conservative.

## VII. Conclusion

The DRA correctly incorporates a 10x safety factor, but contains assumptions, algorithms, and conclusions that are not supported by the available evidence on the toxicity of TCVP and exposures resulting from pet uses and therefore cannot not be relied upon as the basis for evaluating risk to children from TCVP. Remedy of the flaws in the DRA to include setting a benchmark dose at the most sensitive endpoint, evaluation of dermal exposure, utilization of residue data from the Davis Study, and proper characterization of the formulation of the flea collar will identify exposures which do not meet the safety standard. NRDC urges EPA to grant its petition and begin cancellation proceedings for TCVP for use in household pet products.

Message

**From**: Taylor, Linda [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CBFA6AA22DAF4AF8BA2E13991525A046-LINDA TAYLOR]
**Sent**: 11/21/2016 4:18:18 PM
**To**: Personal Matters / Ex. 6
**Subject**: hed
**Attachments**: Inhalation piece.docx

Message

**From**: EPA Pesticides Programs [oppt.epa@public.govdelivery.com]
**Sent**: 1/4/2017 7:17:33 PM
**To**: Vogel, Dana [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8fa57c9380b2438895809b525dd668ea-Dana Vogel]
**Subject**: Pesticide Program Update: EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pet

# EPA Pesticide Program Updates

*From EPA's Office of Pesticide Programs*

*www.epa.gov/pesticides*

January 4, 2017

## In This Update:

### EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pets

EPA has finalized the human health risk assessment of tetrachlorvinphos (TCVP). TCVP is an organophosphate insecticide used to control fleas, ticks, and other pests on and around pets and livestock. It is used in residential products like pet collars.

Through the publication of the revised human health risk assessment and related documents, we are addressing a 2009 Natural Resource Defense Council (NRDC) petition.

This risk assessment identified potential risks to people, including children, in residential settings and to certain workers applying TCVP, which exceed the Agency's level of concern.

The Agency has contacted the pesticide manufacturers to initiate discussions with them to reduce exposure and resolve potential risks identified in the human health risk assessment. The Agency will issue a Proposed Decision in 2017 for public comment. Until that time, it is important to follow label instructions on proper use of pesticide products.

We advise consumers to take certain precautions when handling TCVP products in residential areas. These precautions are listed on TCVP product labels, including:

- not allowing children to play with TCVP pet collar products,
- keeping TCVP spray and powder products out of reach of children, and
- washing hands thoroughly with soap and water after handling.

To view TCVP's human health risk assessment and other registration review documents, visit regulations.gov, docket number EPA-HQ-OPP-2008-0316.

More information on:

- tetrachlorvinphos
- protecting your pets form fleas and ticks
- reducing your child's chances of pesticide poisoning

EPA distributes its Pesticide Program Updates to external stakeholders and citizens who have expressed an interest in the agency's pesticide program activities and decisions. This update service is part of EPA's continuing effort to improve public access to federal pesticide information.

For general questions about pesticides and pesticide poisoning prevention, contact the National Pesticide Information Center (NPIC), by email at npic@ace.orst.edu or, by visiting http://npic.orst.edu.

For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: http://www.epa.gov/pesticides.

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Message

**From**: EPA Pesticides Programs [oppt.epa@public.govdelivery.com]
**Sent**: 1/4/2017 7:17:33 PM
**To**: Wakefield, Benjamin J. [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b2756b86404b49448581918fd2fbc13c-BWAKEFIE]
**Subject**: Pesticide Program Update: EPA Finalizes Human Health Risk Assessment for Pesticide Used on Pet

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*From EPA's Office of Pesticide Programs*

*www.epa.gov/pesticides*

January 4, 2017

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For information about ongoing activities in the Office of Pesticide Programs, visit our homepage at: http://www.epa.gov/pesticides.

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Message

**From**: Zilioli, Erica (ENRD) [Erica.Zilioli@usdoj.gov]
**Sent**: 3/2/2017 8:39:53 PM
**To**: 'Fein, Ian' [ifein@orrick.com]; Wakefield, Benjamin J. [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b2756b86404b49448581918fd2fbc13c-BWAKEFIE]
**CC**: mwu@nrdc.org; ianfein@gmail.com
**Subject**: RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

**Flag**: Follow up

Hi Ian,

Congratulations on making a move! Please send us your new contact info once you have it.

I am pretty swamped this week getting some filings done in another case but I will confer with EPA about the status of TCVP and hopefully get back to you with an update early next week.

Thanks,
Erica

Erica M. Zilioli
U.S. Department of Justice
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Washington, DC 20044
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**From:** Fein, Ian [mailto:ifein@orrick.com]
**Sent:** Tuesday, February 28, 2017 5:05 PM
**To:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>
**Cc:** Zilioli, Erica (ENRD) <EZilioli@ENRD.USDOJ.GOV>; mwu@nrdc.org; ianfein@gmail.com
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Hi Ben and Erica,

I hope you've both been well. I wanted to thank you again for giving us a head's up about the TCVP Risk Assessment back in December, and also to check in and see whether you had any further updates on the process.

Is it still EPA's intention to issue a final revised response to NRDC's 2009 petition within 90 days of the December issuance of the Risk Assessment?

Also, I am leaving my current firm but will continue to be working with NRDC on this case. So for future correspondence on this matter, please email me at ianfein@gmail.com.

Many thanks again,
Ian

**From:** Wakefield, Benjamin J. [mailto:wakefield.benjamin@epa.gov]
**Sent:** Wednesday, December 28, 2016 3:39 PM
**To:** Fein, Ian <ifein@orrick.com>
**Cc:** Erica Zilioli <Erica.Zilioli@usdoj.gov>; mwu@nrdc.org
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Ian,

It is EPA's current intention and belief that the Agency will issue a final revised response to NRDC's 2009 petition to cancel all pet uses of TCVP within 90 days of issuing the Revised Human Health Risk Assessment for Registration Review.

The Revised Risk Assessment is not yet public, and it will speak for itself regarding the Davis Study when it is posted to the regulations.gov docket.

I do not currently have a precise estimate of when the Proposed Interim Decision is likely to be published.

Have a Happy New Year.

Regards,

- Ben

Benjamin J. Wakefield
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**From:** Fein, Ian [mailto:ifein@orrick.com]
**Sent:** Wednesday, December 28, 2016 6:22 PM
**To:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>
**Cc:** Erica Zilioli <Erica.Zilioli@usdoj.gov>; mwu@nrdc.org
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Thanks so much for the heads up, Ben. We really appreciate it. I hope you and Erica have both had a wonderful holidays so far.

Now that the risk assessment has been finalized, does EPA still plan to revise its response to NRDC's cancellation petition within 90 days?

Also, we saw the document posted on the docket last week about EPA's decision to rely on the Davis Study. Will the risk assessment discuss the "more stringent regulatory decisions" referenced in that document, or will that be in the Proposed Interim Decision (PID) instead? And do you know when in 2017 the PID will likely be published for public comment?

Thanks again for reaching out. I hope you and Erica each have a wonderful time away from the office.

Best,
Ian

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**From:** Wakefield, Benjamin J. [mailto:wakefield.benjamin@epa.gov]
**Sent:** Wednesday, December 28, 2016 12:39 PM
**To:** Fein, Ian <ifein@orrick.com>; mwu@nrdc.org
**Cc:** Erica Zilioli <Erica.Zilioli@usdoj.gov>
**Subject:** Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Ian and Mae,

The Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment for Registration Review has been finalized and is in the process of being posted to the TCVP registration review docket at regulations.gov (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2008-0316). Although the revised risk assessment does not yet appear to be posted to the docket, I expect that it will be in the next few days.

I will be out of the office starting tomorrow, returning Tuesday, January 3rd. Erica is out until Monday, January 9th. Since both of us will likely be out of the office when the document posts to the docket, I wanted to let you know that the document has been finalized in case you wish to monitor the docket for its posting.

Regards,

- Ben Wakefield

---

Benjamin J. Wakefield
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Office of General Counsel, Pesticides & Toxic Substances Law Office
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**From:** Zilioli, Erica (ENRD) [mailto:Erica.Zilioli@usdoj.gov]
**Sent:** Tuesday, June 14, 2016 2:45 PM
**To:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>
**Subject:** FW: TCVP case

FYI.

---

**From:** Weaver, Susannah Landes [mailto:sweaver@orrick.com]
**Sent:** Tuesday, June 14, 2016 2:39 PM
**To:** Zilioli, Erica (ENRD) <EZilioli@ENRD.USDOJ.GOV>
**Cc:** Fein, Ian <ifein@orrick.com>
**Subject:** TCVP case

Hi Erica,

I hope you're doing well. I wanted to let you know that I will be leaving Orrick tomorrow to join Donahue & Goldberg. For any further communications on the TCVP matter, Ian Fein (cc'd here) will be the point person.

Best,
Susannah

ORRICK

SUSANNAH LANDES WEAVER
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Message

**From**: Zilioli, Erica (ENRD) [Erica.Zilioli@usdoj.gov]
**Sent**: 3/9/2017 11:19:15 PM
**To**: Ian Fein [ianfein@gmail.com]
**CC**: Wakefield, Benjamin J. [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b2756b86404b49448581918fd2fbc13c-BWAKEFIE]; mwu@nrdc.org
**Subject**: RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

**Flag**: Follow up

Hi Ian,

EPA currently intends to send something to NRDC by March 21st.

Thanks,
Erica

Erica M. Zilioli
U.S. Department of Justice
Environmental Defense Section
P.O. Box 7611
Washington, DC 20044
202.514.6390

---

**From:** Ian Fein [mailto:ianfein@gmail.com]
**Sent:** Thursday, March 02, 2017 11:25 PM
**To:** Zilioli, Erica (ENRD) <EZilioli@ENRD.USDOJ.GOV>
**Cc:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>; mwu@nrdc.org
**Subject:** Re: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Thank you so much, Erica. Next week would be great.

I should have new contact info soon, and will pass it along when I do. In the meantime, you can reach me at this email address and my cell phone, 415-367-5062.

Thanks again,
Ian

On Mar 2, 2017, at 12:39 PM, Zilioli, Erica (ENRD) <Erica.Zilioli@usdoj.gov> wrote:

> Hi Ian,
>
> Congratulations on making a move! Please send us your new contact info once you have it.
>
> I am pretty swamped this week getting some filings done in another case but I will confer with EPA about the status of TCVP and hopefully get back to you with an update early next week.
>
> Thanks,
> Erica

Erica M. Zilioli
U.S. Department of Justice
Environmental Defense Section
P.O. Box 7611
Washington, DC 20044
(202) 514-6390
erica.zilioli@usdoj.gov

---

**From:** Fein, Ian [mailto:ifein@orrick.com]
**Sent:** Tuesday, February 28, 2017 5:05 PM
**To:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>
**Cc:** Zilioli, Erica (ENRD) <EZilioli@ENRD.USDOJ.GOV>; mwu@nrdc.org; ianfein@gmail.com
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Hi Ben and Erica,

I hope you've both been well. I wanted to thank you again for giving us a head's up about the TCVP Risk Assessment back in December, and also to check in and see whether you had any further updates on the process.

Is it still EPA's intention to issue a final revised response to NRDC's 2009 petition within 90 days of the December issuance of the Risk Assessment?

Also, I am leaving my current firm but will continue to be working with NRDC on this case. So for future correspondence on this matter, please email me at ianfein@gmail.com.

Many thanks again,
Ian

---

**From:** Wakefield, Benjamin J. [mailto:wakefield.benjamin@epa.gov]
**Sent:** Wednesday, December 28, 2016 3:39 PM
**To:** Fein, Ian <ifein@orrick.com>
**Cc:** Erica Zilioli <Erica.Zilioli@usdoj.gov>; mwu@nrdc.org
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Ian,

It is EPA's current intention and belief that the Agency will issue a final revised response to NRDC's 2009 petition to cancel all pet uses of TCVP within 90 days of issuing the Revised Human Health Risk Assessment for Registration Review.

The Revised Risk Assessment is not yet public, and it will speak for itself regarding the Davis Study when it is posted to the regulations.gov docket.

I do not currently have a precise estimate of when the Proposed Interim Decision is likely to be published.

Have a Happy New Year.

Regards,

- Ben

Benjamin J. Wakefield
U.S. Environmental Protection Agency
Office of General Counsel, Pesticides & Toxic Substances Law Office
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Washington, D.C. 20460
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**From:** Fein, Ian [mailto:ifein@orrick.com]
**Sent:** Wednesday, December 28, 2016 6:22 PM
**To:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>
**Cc:** Erica Zilioli <Erica.Zilioli@usdoj.gov>; mwu@nrdc.org
**Subject:** RE: Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Thanks so much for the heads up, Ben. We really appreciate it. I hope you and Erica have both had a wonderful holidays so far.

Now that the risk assessment has been finalized, does EPA still plan to revise its response to NRDC's cancellation petition within 90 days?

Also, we saw the document posted on the docket last week about EPA's decision to rely on the Davis Study. Will the risk assessment discuss the "more stringent regulatory decisions" referenced in that document, or will that be in the Proposed Interim Decision (PID) instead? And do you know when in 2017 the PID will likely be published for public comment?

Thanks again for reaching out. I hope you and Erica each have a wonderful time away from the office.

Best,
Ian

---

**From:** Wakefield, Benjamin J. [mailto:wakefield.benjamin@epa.gov]
**Sent:** Wednesday, December 28, 2016 12:39 PM
**To:** Fein, Ian <ifein@orrick.com>; mwu@nrdc.org
**Cc:** Erica Zilioli <Erica.Zilioli@usdoj.gov>
**Subject:** Tetrachlorvinphos (TCVP) Revised Human Health Risk Assessment

Ian and Mae,

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- Ben Wakefield

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**Sent:** Tuesday, June 14, 2016 2:45 PM
**To:** Wakefield, Benjamin J. <wakefield.benjamin@epa.gov>
**Subject:** FW: TCVP case

FYI.

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**To:** Zilioli, Erica (ENRD) <EZilioli@ENRD.USDOJ.GOV>
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**Subject:** TCVP case

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Best,
Susannah

<image001.gif>

SUSANNAH LANDES WEAVER
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Appointment

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/16/2017 5:15:18 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]; Nguyen, Khue [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53463f4f956d4772a6ada2f68debfcb8-Nguyen, Khue]; Biggio, Patricia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2a9a640a9a2941c5a9be1c4967e71718-Biggio, Pat]

**Subject**: Tetrachlorvinphos HED Revised Risk Assessment Discussion
**Attachments**: TCVP revised human health assessment dec2016.pdf; TCVP PID Mitigation Proposal 1.10.17.docx; TCVP RA one-pager 1.31.17..docx
**Location**: DCRoomPYS9671/Potomac-Yard-One

**Start**: 2/16/2017 9:00:00 PM
**End**: 2/16/2017 9:30:00 PM
**Show Time As**: Busy

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM**

**Date:** December 21, 2016

**SUBJECT:** **Tetrachlorvinphos (TCVP)** Revised Human Health Risk Assessment for Registration Review

**PC Code:** 083701, 083702
**Petition No.:** NA
**Risk Assessment Type:** Single Chemical Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** 436834
**Registration Nos.:** NA
**Regulatory Action:** Registration Review
**Case No.:** 1321
**CAS No.:** 22248-79-9
**40 CFR:** §180.252

**FROM:** Danette Drew, Chemist
Linda Taylor, Ph.D. Toxicologist
Kelly Lowe, Environmental Scientist
Risk Assessment Branch V/VII
Health Effects Division (HED, 7509P)

And

Wade Britton, MPH, Environmental Health Scientist
Risk Assessment Branch IV
Health Effects Division (HED, 7509P)

**THROUGH:** Michael Metzger, Branch Chief
Risk Assessment Branch V/VII
Health Effects Division (HED, 7509P)

**TO:** James Parker, Chemical Review Manager
Neil Anderson, Branch Chief
Risk Management and Implementation Branch I
Pesticide Re-evaluation Division (7508P)

Attached is HED's revised human health risk assessment in support of the registration review of the insecticide tetrachlorvinphos (TCVP).



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## 1.0 Executive Summary

The insecticide tetrachlorvinphos (TCVP) [(Z)-2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate] is a member of the organophosphate (OP) class of pesticides. TCVP is used as a dermal or oral treatment to livestock (i.e., cattle, swine, poultry and horses) and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs. Formulations for pet use include collars, dusts/powders, and pump and trigger sprays. The other (non-pet) uses include dusts (D), emulsifiable concentrates (EC), feed through (solid and liquid food additives), feed blocks, and wettable powders (WP). Human exposure to TCVP in food may occur as a result of consuming residues in animal commodities (e.g., meat). Exposure may also occur from drinking water that may contain TCVP residues as a result of some outdoor use patterns. Residential exposures may occur as a result of applying flea products to pets (cats and dogs) or contacting treated pets. Occupational exposures may occur during application of TCVP to livestock or their premises, or during outdoor perimeter or kennel treatments. Occupational exposures may also occur to veterinarians and pet groomers. Exposure via spray drift is not anticipated based on the current use patterns.

The most recent human health risk assessment for TCVP was completed in December 2015 (D. Drew *et al.*, 12/21/2015, *Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review*, D411095). The current TCVP risk assessment reflects the following changes since the 2015 risk assessment:

- The reduction of the oral toxicological point of departure (POD) from 8.0 mg/kg/day to 2.8 mg/kg/day based on additional red blood cell (RBC) acetylcholinesterase (AChE) inhibition data identified during this re-evaluation in the current acute comparative cholinesterase assay (CCA) study in rats.

- The use of the literature study, Davis, M. et al., *Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos.* Journal of Exposure Science and Environmental Epidemiology ((2008) 18, 564-57), (*hereinafter* Davis study), following approval for its use in risk assessment by the Human Studies Review Board (HSRB) in January 2016. Previously, risk estimates from both a surrogate residue transfer study (i.e., an amitraz pet collar study[1]) and the Davis literature study were presented. HED is now relying solely on the Davis study data since these chemical-specific data have been approved by the HSRB for use and result in a higher estimated exposure potential (i.e., are more health protective) than the surrogate data.

- Following a reassessment of the mutagenicity data available on TCVP, the relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be

[1] MRID 49468801: *Determination of Transferable Residues of Amitraz from the Hair of Dogs Following the Application of the Preventic® Collar.*

established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[2].

- Following the Dec. 21, 2015 TCVP risk assessment, information was submitted during the public comment period to address whether the active ingredients in TCVP pet collars are released as a liquid or solid (dust) form, or both. The submitted information describes that both a liquid and particulate, or dust, are present on the surface of the pet collar. Therefore, HED has assumed that TCVP could be transferred in either form from the collar to the pet's fur and result in the potential for post-application exposures from contact with the treated pet. HED has assessed exposures resulting from the TCVP pet collar uses assuming that the TCVP pet collar product exists as a liquid and solid form concurrently at varying ratios (e.g., 1/99, 50/50, and 99/1 liquid/dust). [See Section 6.0 of this document for a complete description of this approach].

This document also addresses, where appropriate, the comments received during the public comment period following publication of the 2015 TCVP draft human health risk assessment. A comprehensive response to comments received is also provided in the following memo: D. Drew et al., *Tetrachlorvinphos (TCVP) Health Effects Division Response to Comments on the December 21, 2015 Draft Human Health Risk Assessment for TCVP Registration Review*, D433403, 12/21/2016).

*Hazard*

TCVP is a member of the OP class of pesticides. For TCVP, like other OPs, the initiating event in the adverse outcome pathway/mode of action (AOP/MOA) involves inhibition of the enzyme acetylcholinesterase (AChE) *via* phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For TCVP, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. TCVP does not require metabolic activation to an oxon to inhibit AChE; i.e., the parent compound is the active form inhibiting AChE. OPs generally exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same dose, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks; a pattern that is observed for most OPs, but not every OP, like TCVP, which shows no difference in response across duration. For TCVP the steady state is

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[2] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.



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reached after a single day of exposure. As such, the endpoint selection for TCVP considers data available for all durations of dosing when choosing the most protective point of departure.

The toxicology database for TCVP is complete except the requirement for additional mutagenicity studies [a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and an assay that examines possible genotoxic activity in the target (liver) organ] (McCarroll, 2016; TXR No. 0057226)[3]. TCVP has cholinesterase data across multiple lifestages, durations, and routes for both red blood cell (RBC) and brain cholinesterase inhibition. There are acceptable studies available for toxicity endpoint and point of departure (POD) selection. For TCVP, RBC AChE inhibition is the most sensitive endpoint and is the endpoint from which the PODs for all TCVP exposure routes and durations were selected.

There is no evidence of quantitative or qualitative sensitivity in the developmental rat and rabbit studies or in the gestational (fetus) or juvenile components of the comparative cholinesterase assay (CCA) studies in rats. AChE data from the CCA studies suggest that the fetus is not more sensitive than the pregnant dam, and that pregnant females are not more sensitive than non-pregnant females with respect to cholinesterase inhibition. When comparing RBC $BMD_{10}$ (benchmark dose) estimates from across the acute (single dose) CCA and repeat dose CCA studies, it is apparent that there are no age-related (or duration-related) differences. The acute and steady state PODs selected for oral exposure risk assessment are based on RBC AChE inhibition in the postnatal day 11 (PND11) and postnatal day 21 (PND21) pups in the acute CCA since they provide the most robust dose-responses and are protective of all life stages. Although the steady state dietary POD was selected from an acute CCA, the acute study is considered appropriate for longer term durations since AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose.

High quality AChE data for the dermal and inhalation routes are also available and allow for route specific evaluation. RBC AChE inhibition was observed in both sexes in the inhalation study (brain AChE was not assessed), while no inhibition of RBC or brain AChE was observed in the dermal study up to the limit dose. A non-cancer dermal assessment is not required for TCVP; however, a cancer dermal assessment is required. The dermal absorption factor is 9.6% for TCVP.

TCVP is classified as a Group C possible human carcinogen (based on statistically significant increases in combined hepatocellular adenoma/carcinoma in female mice) with a linear low-dose approach for quantification of risk using the oral slope factor (Q1*) of $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$. Whereas parent compound TCVP is the residue of concern for AChE inhibition, TCVP plus metabolites containing the 2,4,5 trichlorobenzene moiety are the residues of concern for cancer assessment. Following a reassessment of the mutagenicity data available on TCVP, it was determined that the relevance of the mutagenic findings to the tumorigenic response seen in

---

[3] *Ibid.*



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female mice cannot be established. Following the submission and review of the required mutagenicity assays, the need for an updated cancer assessment will be determined.

For TCVP, as for other OPs, the FQPA safety factor (SF) of 10X has been retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

For the acute and steady state dietary assessments, a total uncertainty factor of 1000X is appropriate for infants, children, youths and females of childbearing age (10X to account for interspecies extrapolation and 10X for intraspecies variation and the 10X FQPA SF). The only population subgroup for dietary exposure scenarios for which the FQPA SF is not retained is adults 50-99 years of age; therefore, the total uncertainty factor for that population is 100X.

A total uncertainty factor of 1000X is appropriate for residential incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF). A total uncertainty factor of 300X is appropriate for all inhalation exposures: 3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments (or a 10X database uncertainty factor for occupational assessments to protect potentially pregnant female workers) due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

*Tolerances*

Tolerances for residues of TCVP are established under 40 CFR §180.252 for livestock commodities based on oral feed-through and direct dermal uses on livestock (cattle, swine, and poultry). The residues of concern for tolerance enforcement are tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol (frequently abbreviated as TCVP, TCVPdeme, TCPEol , TCPEone, and TCPEdiol, respectively). The current tolerance expression under 40 CFR §180.252 includes all of these residues except des-O-methyl tetrachlorvinphos; this metabolite should be included in the tolerance expression. The current tolerance levels should be updated in the 40 CFR as discussed in Section 2.2.3.
There are no Codex maximum residue limits (MRLs) established or proposed for residues of TCVP. Canada has established MRLs for plant (apple and grape) and livestock commodities. The differences in U.S. and Canadian residue definitions prohibit harmonization.

*Dietary Risk Assessment*

Acute (TCVP), steady state (TCVP), and cancer (TCVP plus metabolites containing the 2,4,5 trichlorobenzene moiety) dietary (food and drinking water) exposure and risk assessments were conducted using the DEEM-FCID v3.16 model. The dietary exposure analyses for TCVP are mostly refined. The only food forms included in the analyses are based on animal commodities. The food residues were based upon U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) monitoring data except where no appropriate PDP data were available (i.e.,



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residues from poultry dermal application studies were used for poultry fat and skin). The Biological and Economic Analysis Division (BEAD) of OPP provided percent of livestock treated information. Model-derived estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effect Division (EFED). A distribution of EDWCs was used probabilistically in the acute and steady state analyses. For the cancer analysis, the EDWC was included as a single point estimate.

The acute dietary (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 190% of the aPAD. When drinking water is analyzed by itself, the acute dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95$^{th}$ and 99.9$^{th}$ percentile of exposure.

The steady state (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the steady state population adjusted dose (ssPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 120% of the ssPAD. The steady state dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95$^{th}$ and 99.9$^{th}$ percentile of exposure.

*Residential Handler Risk Assessment*

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are assumed to complete all elements of an application without use of any protective equipment.

Residential TCVP handler exposures are anticipated to be short- (1 to 30 days) and intermediate-term (1 to 6 months) in duration. However, because of the steady state AChE inhibition exhibited by the OPs (typically 21 days and longer for OPs, but 1 day to reach steady state for TCVP), steady state exposures were assessed and presented for residential exposures to TCVP pet products. Residential handler exposures to TCVP pet products may occur via the dermal or inhalation routes while the product is placed on a cat or dog. Both steady state non-cancer and cancer residential handler exposure assessments were performed for adult homeowners applying TCVP pet collars, dusts/powders, and pump/trigger sprays products to cats and dogs. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are assessed.

<u>Residential Handler Steady State (Non-Cancer):</u>

Pet Collars: Because there is uncertainty as to whether the TCVP pet collars are liquid and/or dust formulated products, residential handler (adult) steady state inhalation exposures were evaluated assuming both liquid and dust residues are present simultaneously at varying ratios



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(e.g., 1/99, 50/50, and 99/1 liquid/dust). Unit exposure (UE) data (for handler exposure), and residue transfer data and transfer coefficients (for post-application exposure) specific to each formulation type were used. For handlers, the liquid formulation assessment used spot-on surrogate UE data, which assumes negligible inhalation exposure; therefore, only the dust-specific UE data (i.e., a TCVP dust/powder applicator exposure study) is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure. No non-cancer inhalation risks of concern were identified for residential handlers for any liquid/dust formulation ratio assumption (all MOEs ≥ level of concern (LOC) of 300). When assuming a ratio of 1/99 liquid/dust, MOEs range from 920 to 4,600; when assuming a ratio of 50/50 liquid/dust, MOEs range from 1,800 to 9,100; and when assuming a ratio of 99/1 liquid/dust, MOEs range from 91,000 to 450,000.

Dust/Powder and Pump/Trigger Spray: All residential handler (adult) non-cancer steady state inhalation risks estimated for the TCVP pet dust/powder and pump/trigger spray formulations are not of concern (i.e., all MOEs are > 300; LOC = 300; range = 3,200 to 160,000).

Residential Handler Cancer:

Pet Collars: Residential handler cancer risks (combined dermal and inhalation) estimated for TCVP pet collars assuming 1/99 and 50/50 liquid/dust formulation ratios are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$.

Dust/Powder and Pump/Trigger Spray: Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$.

*Residential Post-Application Risk Assessment*

There is the potential for post-application exposure for individuals exposed as a result of contacting a cat or dog previously treated with TCVP pet products (dusts/powders, pump/trigger sprays, pet collars). Since there is no non-cancer dermal hazard for TCVP, a quantitative non-cancer post-application dermal exposure assessment was not performed for adults or children. A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from applications to pets. The quantitative exposure/risk assessment for residential post-application exposures is based on incidental oral (hand-to-mouth) exposure to children (1 to < 2 years old) from contacting cats and dogs treated with TCVP. While not the only lifestage potentially exposed for these post-application scenarios, this lifestage is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential TCVP post-application exposures are anticipated to be short- (1 to 30 days), intermediate-term (1 to 6 months), and long-term (>6 months – *for pet collar scenarios only*) in duration. However, because of the steady state AChE inhibition exhibited by the OPs, steady state exposures were assessed and presented for residential exposures to TCVP pet products.



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Residential Post-Application Steady State (Non-Cancer):

Pet Collars: As was done for residential handlers, due to the uncertainty as to whether the TCVP pet collars are liquid and/or dust formulated products, residential post-application exposures were evaluated assuming both liquid and dust residues are present simultaneously at varying ratios (e.g., 1/99, 50/50, and 99/1 liquid/dust). For post-application exposure from pet collars, the same data were used to estimate transferable residues for both liquid and dust formulations; however, the transfer coefficients used to assess potential post-application exposure to dust formulations are much higher compared to those used for liquid formulations. Therefore, as with handlers, the post-application risk estimates are driven by the presence of dust in the formulations. Children's incidental oral (hand-to-mouth) steady state exposures to pets treated with TCVP collars are estimated to be of concern regardless of the ratio of liquid/dust assumed (i.e., MOEs < 1000; LOC = 1000). When assuming a 1/99 liquid/dust formulation ratio, MOEs range from 0.91 to 7.4. When assuming a 50/50 liquid/dust formulation, MOEs range from 1.8 to 15, and when assuming a 99/1 liquid/dust formulation, MOEs range from 65 to 530.

Dust/Powder and Pump/Trigger Spray: Children's incidental oral (hand-to-mouth) steady state exposures to pets treated with TCVP dust/powders are estimated to be of concern (MOEs range from 98 to 640; LOC = 1000). However, children incidental oral exposures to pets treated with TCVP pump/trigger spray products are estimated not to be of concern (i.e., MOEs are > 1000; MOEs range from 1,600 to 15,000).

Residential Post-Application (Cancer):

Pet Collars: Residential post-application cancer (adult; dermal only as post-application inhalation exposure is negligible for this use) risk estimates for TCVP pet collars assuming 1/99 or 50/50 liquid/dust formulation ratios range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1 liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$.

Dust/Powder and Pump/Trigger Spray: Residential post-application cancer (adult; combined dermal and inhalation) risks estimated for TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$.

*Spray Drift*

A quantitative spray drift assessment was not conducted because the use of TCVP for direct animal treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs are either 1) not applied via aircraft, groundboom, or airblast equipment or 2) for applications to poultry buildings with groundboom equipment, the use is indoors and not anticipated to be a significant source of spray drift.

*Aggregate Risk Assessment*

The acute aggregate risk assessment combines exposures to TCVP from food and drinking water. There are acute risk estimates of concern for food only; therefore, a quantitative acute aggregate

risk assessment was not conducted. The steady state aggregate assessment includes the steady state dietary (food and drinking water) and residential exposures. However, because there are risks of concern associated with both dietary (food) and residential exposure, a quantitative steady state aggregate risk assessment was not conducted. If mitigation occurs such that the risks for the individual contributors to the aggregate risk are acceptable, a quantitative assessment may be completed at that time.

The cancer aggregate risk assessment combines residential and dietary (food and drinking water) expected lifetime exposures for adults. For TCVP, a cancer aggregate assessment was performed for adult handlers and for adult post-application activities related to residential pet product use.

The residential handler cancer aggregate assessment uses exposures from applying TCVP products to pets. The cancer aggregate assessment combines the highest (worst case, upper bound) handler exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type. The cancer aggregate (dietary and residential exposures) risk estimates for handlers for the upper bound exposures for collars, dust/powders, and pump/trigger sprays are in the $10^{-7}$ to $10^{-6}$ range

The residential post-application cancer aggregate assessment uses exposures from contacting pets treated with TCVP products. The cancer aggregate assessment combines the highest (worst case, upper bound) post-application exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type. The cancer aggregate (dietary and residential exposures) post-application risk estimates for the upper bound exposures for collars, dust/powders, and pump/trigger sprays range from $10^{-6}$ to $10^{-4}$.

*Occupational Handler Risk Assessment*

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. Occupational handler exposures to TCVP may occur via the dermal or inhalation routes while the mixing/loading and applying products registered for dermal or oral treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs (professional pet handlers).

Occupational handler exposure is expected to be short- and intermediate-term in duration. However, because of the steady state AChE inhibition exhibited by the OPs, steady state exposures were assessed and presented for occupational exposures to TCVP products. Both steady state non-cancer and cancer handler exposure assessments were performed. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment

includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are assessed.

Occupational Handler Steady State (Non-Cancer):

Of the 198 total occupational handler exposure scenarios assessed, the majority (162) are not of concern (i.e., steady state inhalation MOEs are $\geq 300$; LOC = 300) with currently required personal protective equipment (PPE) (i.e., respiratory protection). Of the remaining 36 handler exposure scenarios, an additional 25 are not of concern with consideration of increasing levels of respiratory protection (i.e., 11 occupational handler exposure scenarios result in estimated risks of concern despite the addition of respiratory protection or engineering controls).

Occupational Handler Cancer:

Occupational cancer risks were estimated for both private/farmer and contract/commercial handlers. Cancer risk estimates, with currently required PPE, range from $10^{-10}$ to $10^{-5}$ for private/farmer handlers and from $10^{-10}$ to $10^{-4}$ for contract/commercial handlers.

*Occupational Post-Application Risk Assessment*

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties.

Occupational post-application exposures are not anticipated for TCVP as the majority of application scenarios are not to foliar surfaces. The use of TCVP outdoors as a perimeter treatment is not expected to result in occupational post-application exposure as reentry activities related to crop production (e.g., scouting, harvesting) are not anticipated for this use pattern.

*Human Studies Review*

This risk assessment relies in part on data from studies in which human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from Pesticide Handler Exposure Database (PHED) 1.1; the AHETF database; the Residential SOPs (Treated Pets); as well as a TCVP dust/powder applicator exposure study (MRID 45519601), a mixer/loader/applicator wettable powder study (MRID 42622301), and TCVP dust and pump spray study (MRID 45485501): (1) are subject to ethics review pursuant to 40 CFR Part 26, (2) have received the review necessary for consideration in this risk assessment, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have

included review by the HSRB. Descriptions of data sources, as well as guidance on their use, can be found at the agency website.[4]

Data were also used from a literature study using TCVP pet collars, Davis, M. *et. al., Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos.* Journal of Exposure Science and Environmental Epidemiology. (2008) 18, 564-57). On January 12-13, 2016 the EPA HSRB met to address the scientific and ethical charge questions related to the Davis study. The HSRB concluded that, "the research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol used in the study can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars."[5]

*CropLife America Petition*

On November 29, 2016, CropLife America (CLA) submitted a petition to EPA asking the agency to "halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner." Any interim or final registration review decision for TCVP could potentially be impacted by EPA consideration of the epidemiological studies identified in the CLA petition. EPA is therefore placing a copy of the CLA petition in the registration review docket for TCVP. In the near future, EPA intends to publish a notice on its Pesticide Website announcing the receipt of the CLA petition and opening a comment period on the petition. Persons wishing to comment on the petition should respond to EPA in connection with that comment period.

## 2.0 HED Recommendations

### 2.1 Data Deficiencies

A follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and a study that investigates possible genotoxic activity in the target organ (liver) are required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target).

Based on the findings from the mutagenicity revisit, HED is recommending that TCVP be assayed in a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395)

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[4] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

[5] Letter from Liza Dawson, PhD, Chair of the EPA HSRB to Thomas Burke, PhD, MPH, EPA Science Advisor. Subject: January 12-13, 2016 EPA Human Studies Review Board Meeting Report. March 30, 2016.

using both sexes, an appropriate sample size (5/sex/dose/sacrifice time) and oral treatment (dietary would be the best fit for the risk assessment). HED further recommends that the assay should cover the range of doses used in the 1980 Hazleton study (MRID 00117443) that will span the tumorigenic dose range for both sexes and the conditions should simulate conditions in the Amer et al., 1983 study. An additional study which would investigate possible genotoxic activity in the target organ (*i.e.,* mouse liver) should be performed. This assay with the target tissue would be appropriate and should follow a similar protocol as described above and should examine DNA damage potential (*e.g.,* Comet assay, DNA adduct formation or any other DNA target)[6].

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

A gas liquid chromatography (GLC) method for the determination of TCVP *per se* in livestock commodities is described in the Pesticide Analytical Method (PAM), Vol. II, as Method I.

The registrant has submitted a method (14020.6106) for the determination of tetrachlorvinphos and its metabolites (TCVPdeme, TCPEdiol, TCPEone and TCPEol) in livestock commodities, which uses QuEChERS and LC/MS/MS methods. The test data for method 14020.6106 are classified as scientifically acceptable for use as an analytical method for ruminant and poultry commodities.

The submitted multiresidue method testing data are acceptable and indicate that FDA multiresidue methods are not suitable for analysis of the TCVP metabolites TCPEdiol and TCVPdeme. However, the metabolites TCPEol and TCPEone were recoverable under Protocol F, although fortified recoveries were small (<50%).

It should be noted that the FDA PESTDATA database dated 8/93 (PAM Vol. I, Appendix II) indicates that parent compound TCVP is completely recovered (>80%) using FDA multiresidue method protocol D (section 232.4) but is not recovered using protocol E (Sections 211.1/231.1 and 212.1/232.1, fatty and nonfatty matrices).

### 2.2.2 International Harmonization

There are no Codex maximum residue limits (MRLs) established or proposed for residues of TCVP. Canada has established MRLs for plant (apple and grape) and livestock commodities. The U.S. tolerances are for livestock commodities; there are no registered crop uses. Canada's residue definition is 2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate (TCVP) and its

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[6] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

low melting isomer as opposed to the U.S. definition which includes the parent compound TCVP plus the four metabolites of concern. The differences in U.S. and Canadian residue definitions prohibit harmonization. HED has not examined the Canadian registrations; different use patterns may also be a factor in achieving harmonization. A summary of U.S. and international tolerances and maximum residue limits is presented in Appendix F.

### 2.2.3 Recommended Tolerances

Tolerances for residues of TCVP in livestock commodities are established under 40 CFR §180.252. The current tolerance expression is for the combined residues of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] and its metabolites, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol.

The HED Metabolism Committee has determined that the residues of concern for tolerance enforcement are tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. The current tolerance expression under 40 CFR §180.252 includes all of these residues *except des-O-methyl tetrachlorvinphos*; this metabolite should be included in the tolerance expression. To allow separate risk assessments for 1) cholinesterase inhibition (parent TCVP only) and 2) carcinogenicity (parent plus metabolites), the tolerances for each livestock commodity should also specify the maximum residues of TCVP *per se* from the total residues. The tolerance definition should be modified as follows, to be consistent with the Tolerance Expression Guidance issued 5/27/09 (S. Knizner).

Tolerances are established for residues of the insecticide tetrachlorvinphos, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate) and its metabolites chloro- 1 -(2,4,5-trichlorophenyl)-vinylmonomethyl phosphate, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol, calculated as the stoichiometric equivalent of tetrachlorvinphos, in or on the commodity.

**Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos.**

| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
|---|---|---|---|---|
| Cattle, fat (of which no more than 0.1 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat | 1.0 | *Cattle, fat (of which no more than 0.6 ppm is tetrachlorvinphos per se)* |

| Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos. | | | | |
|---|---|---|---|---|
| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
| Cattle, kidney (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 1.0 | -- | Remove | See cattle, meat byproducts |
| Cattle, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.5 | -- | Remove | |
| Cattle, meat (of which no more than 2.0 ppm is tetrachlorvinphos *per se*) | 2.0 | 0.27 (0.21) muscle | 0.3 | *Cattle, meat (of which no more than 0.2 ppm is tetrachlorvinphos per se)* |
| Cattle, meat by products, except kidney and liver | 1.0 | -- | Remove | See cattle, meat byproducts |
| Cattle, meat by products | None | 0.16 (<0.01) liver; 0.28 (0.015) kidney; 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat; 0.27 (0.21) muscle | 1.0 | *Cattle, meat byproducts (of which no more than 0.6 ppm is tetrachlorvinphos per se)* [5] |
| Egg (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.288 (0.026) | 0.3 | *Egg (of which no more than 0.03 ppm is tetrachlorvinphos per se)* |
| Hog, fat (of which no more than 0.1 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat | 1.0 | *Hog, fat (of which no more than 0.6 ppm is tetrachlorvinphos per se)* |
| Hog, kidney (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 1.0 | -- | Remove | See hog, meat byproducts |
| Hog, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.5 | -- | Remove | |
| Hog, meat (of which no more than 2.0 ppm is tetrachlorvinphos *per se*) | 2.0 | 0.27 (0.21) muscle | 0.3 | *Hog, meat (of which no more than 0.2 ppm is tetrachlorvinphos per se)* |
| Hog, meat byproducts, except kidney and liver | 1.0 | -- | Remove | See hog, meat byproducts |
| Hog, meat by products | None | 0.16 (<0.01) liver; 0.28 (0.015) kidney; 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat; 0.27 (0.21) muscle | 1.0 | *Hog, meat byproducts (of which no more than 0.6 ppm is tetrachlorvinphos per se)* [5] |

| Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos. | | | | |
|---|---|---|---|---|
| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
| Milk, fat (reflecting negligible residues in whole milk and of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.05 | 0.072 (0.036) for milk; 0.078 (<0.01) for cream | 0.1 | *Milk (of which no more than 0.04 ppm is tetrachlorvinphos per se)* |
| Poultry, fat (of which no more than 7.0 ppm is tetrachlorvinphos *per se*) | 7.0 | 1.298 (0.099) abdominal fat | 1.4 | *Poultry, fat (of which no more than 0.1 ppm is tetrachlorvinphos per se)* |
| Poultry, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 2.0 | | Remove | See poultry, meat byproducts |
| Poultry, meat (of which no more than 3.0 ppm is tetrachlorvinphos *per se*) | 3.0 | 0.40 (0.082) muscle | 0.4 | *Poultry, meat (of which no more than 0.1 ppm is tetrachlorvinphos per se)* |
| Poultry, meat byproducts, except liver | 2.0 | -- | Remove | See poultry, meat byproducts |
| Poultry, meat byproducts | None | 0.52 (0.016) liver; 0.58 (0.022) kidney; 0.40 (0.082) muscle; 19.41 (6.03) skin with fat; 1.30 (0.099) abdominal fat | 20 | *Poultry, meat byproducts (of which no more than 6.0 ppm is tetrachlorvinphos per se)* [5] |

[1] Time-limited tolerances; current tolerance expression is for the combined residues of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] and its metabolites, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol; expression should also include des-O-methyl tetrachlorvinphos.

[2] Total residues of tetrachlorvinphos and its metabolites, TCVP-deme, TCPEone, TCPEol (free and conjugated forms), and TCPEdiol (free and conjugated), expressed in terms of parent equivalents; the value in parentheses represents the maximum residues of the parent tetrachlorvinphos.

[3] Reassessed tolerance is based on the maximum residue from the respective magnitude of the residue study; the maximum residues of the parent tetrachlorvinphos are reported in the corrected commodity definition.

[4] The residue data for cattle can be used to set tolerances for hog commodities since residues in hog tissues are not likely to be greater than those in cattle tissues.

[5] According to the 18 July 2007 Minutes of the HED ChemSAC meeting, the guidance document will be revised to include language detailing the use of the highest residue data for any tissue (liver, kidney, fat, skin or muscle) to determine the tolerance for meat byproducts. A single tolerance on "meat byproducts" will be recommended based on that highest residue, and individual tolerances will no longer be set on liver, kidney, or meat byproducts (except liver and kidney).

## 2.3 Label Recommendations

### 2.3.1 Recommendations from Residue Reviews

The following label revisions are recommended based on the application methods and rates used in the tetrachlorvinphos magnitude of the residue studies, which were used to determine the appropriate tolerance levels in livestock commodities (GLN 860.1200 Directions for Use):

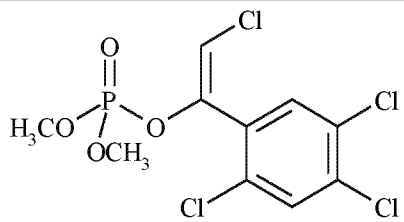
- Based on the magnitude of the residue study on cattle, the product labels with direct animal spray uses on cattle (EPA Reg. Nos. 61483-43 and 61483-50) should be amended to specify a maximum of three applications, with two-week retreatment intervals, at 19 g ai/animal/dose. The product label for Ravap (EPA Reg. No. 61483-50) should also be amended to provide conversion factors to allow calculation of direct animal spray treatment rate in terms of g ai/animal.

- Based on the magnitude of the residue study on poultry, the product labels with direct animal spray uses on poultry (EPA Reg. Nos. 61483-43 and 61483-50) should be amended to specify a maximum of seven applications (with two-week retreatment intervals) at 0.18 g ai/hen/application. Note that the label should specify the weight or volume of the product to be applied.

## 3.0 Introduction

### 3.1 Chemical Identity

**Table 3.1. Tetrachlorvinphos Nomenclature.**

| | |
|---|---|
| Compound |  |
| Common name | Tetrachlorvinphos |
| Company experimental name | TCVP |
| IUPAC name | (Z)-2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate |
| CAS registry number | 22248-79-9 |

See Appendices D and E for nomenclature and physical/chemical properties of TCVP and metabolites (TCVPdeme, TCPEdiol, TCPEone and TCPEol, TCCEol, TCBA).

### 3.2 Physical/Chemical Characteristics

Technical tetrachlorvinphos is a tan to brown crystalline solid with a melting point of 93-98 °C. TCVP is not expected to volatilize significantly due to a low vapor pressure of $2.6 \times 10^{-7}$ torr (25°C). The solubility of tetrachlorvinphos in water at 25°C is 11.6 mg/L. TCVP has limited solubility in most aromatic hydrocarbons. TCVP is hydrophobic, with an octanol-water partition coefficient of 3350 (Log $K_{ow}$ of 3.53).



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### 3.3 Pesticide Use Pattern

TCVP is used as a direct animal treatment to livestock (i.e., cattle, horses, poultry and swine) and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs. The TCVP livestock and perimeter treatment uses are formulated as follows: dusts (D), emulsifiable concentrates (EC), feed through (solid, granular and pelleted/tableted) and liquid food additives), feed blocks, and wettable powders (WP). TCVP can be applied by a variety of means/equipment types including: backrubber/facerubber; backpack; cup; groundboom; handheld fogger; manually-pressurized handwand; mechanically-pressurized handwand; open pour (dust and liquid formulations); paint (airless sprayer or brush/roller); pet collar; plunger; rotary duster; shaker can; spoon; stationary fogger; and trigger spray. For a complete list of registered uses, including maximum use rates, see Appendix A of D436833 (W. Britton, 12/2016, *Tetrachlorvinphos: Final Occupational and Residential Exposure Assessment for Registration Review*).

### 3.4 Anticipated Exposure Pathways

Humans may be exposed to TCVP residues in food since TCVP may be directly applied to, or fed to, livestock which may result in residues in animal commodities. TCVP may reach surface and ground water sources of drinking water through the outdoor usage on poultry droppings, garbage and manure piles, and kennels and corrals. Residential exposures (handler and post-application) may occur as a result of the application to dogs and cats as dust/powders, sprays, or collars. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational post-application exposures are not expected as reentry activities are not anticipated for the registered TCVP uses.

### 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/environmentaljustice/resources/policy/exec_order_12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks

for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

## 4.0 Hazard Characterization and Dose-Response Assessment

TCVP is a member of the organophosphate class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway/mode of action (AOP/MOA) for TCVP involves inhibition of the enzyme AChE *via* phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). TCVP is in the oxon form and does not require bioactivation prior to inhibiting AChE. For TCVP, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating this toxicology database.

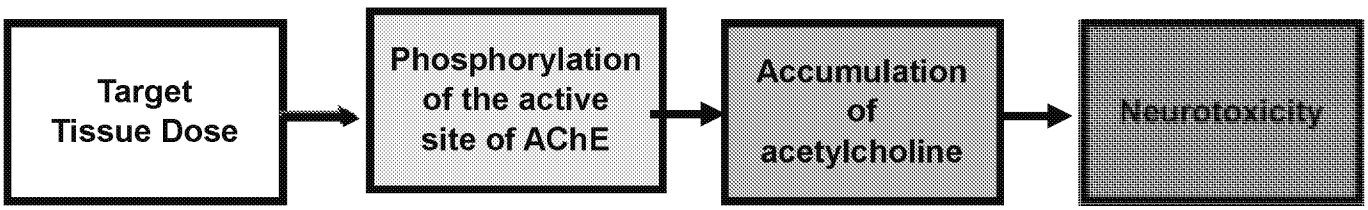


**Figure 1. Adverse outcome pathway for OPs**

### 4.1 Toxicology Studies Available for Analysis

The toxicology database for TCVP is complete except for a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and an *in vivo* assay to examine DNA damage potential (*e.g.,* Comet assay, DNA adduct formation, or any other DNA target)[7].

There are acceptable studies available for toxicity endpoint selection; they include:

- subchronic oral toxicity studies in rats
- chronic oral toxicity studies in rats and dogs
- carcinogenicity studies in rats and mice
- developmental studies in rats and rabbits
- reproduction study in rats

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[7] *Ibid.*

- acute and subchronic neurotoxicity studies in rats
- developmental neurotoxicity (DNT) study in rats
- acute and repeated comparative (CCA) cholinesterase (ChE) studies in juvenile and adult rats
- repeated, gestational ChE study in pregnant rats and fetuses
- delayed neurotoxicity study in hens
- subchronic dermal toxicity study in rats
- repeated dosing inhalation toxicity study in rats
- immunotoxicity study in mice
- complete mutagenicity study battery
- dermal penetration study in rats
- metabolism study in rats

## 4.2 Absorption, Distribution, Metabolism, & Excretion (ADME)

TCVP, unlike some other OPs, does not require metabolic activation to the oxon form to inhibit AChE. In a rat metabolism study, TCVP was almost completely metabolized, and most of the radiolabel was excreted in the urine (46%-60%) and feces (38%-56%) within 48 hours of dosing. Only minor amounts (>0.5%) were found in the tissues. Very little un-metabolized parent compound was recovered. The major metabolite in feces was trichlorophenylethanol, with lesser amounts of trichlorophenylethandiol. The major metabolite in urine was trichloromandelic acid, with lesser amounts of desmethyl tetrachlorvinphos. There is no evidence of bioaccumulation. Some differences in metabolism were noted between the sexes; *e.g.,* males excreted more trichloromandelic acid, a more completely metabolized form of TCVP, whereas females excreted more of the desmethyl TCVP, which could be derived from TCVP with only a single metabolic step.

### 4.2.1 Dermal Absorption

There is a dermal absorption study in rats, which provides a dermal absorption factor (DAF) of 9.6%. In an acceptable *in vivo* dermal penetration study in rats (MRID 42111501), male rats were treated at 0.01, 0.1, 1, and 5 mg/cm$^2$ and sacrificed at 0.5, 1, 2, 4, or 10 hours post dose. Based on total amount of radioactivity recovered from urine, tissues, feces, and carcass after 10 hours of dermal exposure, 84% of the applied dose (0.1 mg/cm$^2$) was recovered in the wash and 9.57% was in the skin, urine, feces, and carcass. The DAF was used to evaluate dermal exposures in the cancer risk assessment. However, since there was no dermal hazard identified for non-cancer endpoints in the dermal toxicity study on TCVP; *i.e.,* no AChE inhibition at the limit dose and no concern for increased susceptibility after repeat exposure, a quantitative dermal assessment was not performed (see Section 4.6.1).

## 4.3 Toxicological Effects



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AChE inhibition is the well-established cholinergic mode of action for OPs and is typically used as the critical effect in hazard characterization for members of this class of pesticides. TCVP inhibits AChE in various species including rats, mice, rabbits, and dogs and is the most sensitive effect in the database. TCVP has AChE data across multiple lifestages (fetal, post-natal, adult), durations (single to 104 weeks), and routes (oral, dermal, inhalation) for both red blood cell (RBC) and brain AChE inhibition. However, when looking at the AChE inhibition data across the numerous studies and datasets, it is apparent that there is no consistent pattern as to the relative sensitivity of the RBC and brain compartments, sex, or life stage. For instance, at a single dose of 10 mg/kg, male RBC and brain AChE were similarly inhibited in both adults (-17% and -13% respectively) and PND11 pups (-14% and -14%, respectively). Additionally, as is observed for some OPs, the oral AChE data demonstrate no increase in inhibition with repeated exposures as compared to a single dose. Specifically, the acute single dose CCA data show $BMD_{10}$ of 6.5, with the 11-day repeated exposure $BMD_{10}$ of 7.7 in adult male rats (see Section 4.3.2).

Transient clinical signs [gait alterations, constricted pupils, tremors (fore- and hindlimb), body cool to the touch, decreased defecation, red material on forelimbs, around eyes, nose, mouth] characteristic of cholinergic toxicity were observed in the acute neurotoxicity rat study, and tremors were observed in pregnant rats in the developmental toxicity study at dose levels 100X higher and 5X higher than those eliciting AChE inhibition, respectively. The hen study was negative for indications of delayed neurotoxicity.

There is no evidence of quantitative or qualitative sensitivity in the developmental rat and rabbit studies or in the rat reproduction study following pre-natal and/or postnatal exposure to TCVP. In the rat developmental toxicity study, no developmental effects were observed in the fetus. Developmental toxicity (increased early resorptions, post-implantation loss, and decreased number of live fetuses) was observed in the rabbit developmental toxicity study at the same dose level where significant toxicity (mortality, abortion) was observed in the maternal rabbit. No reproductive or offspring toxicity was observed in the 2-generation reproductive rat study, but increased adrenal weights were observed in the parental rats.

AChE data from the CCA study suggest that the fetus is not more sensitive than the pregnant dam, and that pregnant females are not more sensitive than non-pregnant females with respect to cholinesterase inhibition. When comparing RBC $BMD_{10}$ estimates from across the repeat (48773401) and acute studies (48773401a), it is apparent that there are no age-related (or duration-related) differences. For instance, the $BMD_{10}$ estimates range from 3.2 mg/kg in PND21 male rats to 5.0 mg/kg in PND11 male rats and to 6.5 mg/kg in adult males in the acute CCA study and from 8.6 mg/kg/day in adult female to 20.5 mg/kg/day in the PND 11 pups in the repeat CCA study. Furthermore, the points of departure (POD) used for risk assessment, which are based on cholinesterase inhibition in the PND11 and PND21 animals, since they provide the most robust BMD and BMDL dose-responses, are protective of all life stages.

In the developmental neurotoxicity study (DNT), quantitative susceptibility was observed in pups (decreased pup weight, decreased relative brain weight/measurements) but only at the high

dose of 200 mg/kg/day where maternal toxicity was not demonstrated. However, a 200 mg/kg/day dose to adult female rats in the repeat dose CCA study resulted in 62% RBC and 57% brain cholinesterase inhibition, indicating significant toxicity occurred in the dam in the DNT at this dose. The 200 mg/kg/day dose to the juvenile rats is 20-fold higher than doses reflecting approximately 10%-20% inhibition in juvenile pups in the CCA study and 70-fold higher than the point of departure. Therefore, when considered in combination with the results from the CCA, the high dose of the DNT is not of concern for risk assessment. The BMDs relied upon from the CCA study are protective of the effects observed in pups at higher doses in the DNT study.

TCVP is classified as a Group C possible human carcinogen with a linear low-dose approach for quantification of risk using the oral slope factor (Q1*) of $1.83 \times 10^{-3}$.

In acute lethality studies, TCVP has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is a slight dermal irritant, a moderate eye irritant, and a dermal sensitizer.

### 4.3.2 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined and focused on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute, single dosing, and repeated dosing studies in laboratory animals for TCVP. This analysis provides the basis for determining which exposure durations are appropriate for assessing the human health risk. Table 4.3.2.1 provides a summary of the representative results from experimental toxicology studies with TCVP.

**Table 4.3.2.1 – TCVP $BMD_{10}$ Results (mg/kg/day) for RBC and Brain AChE Inhibition Over Time in Adult Rats**

| MRID (study) | Days of Dosing | % inhibition at LOAEL (mg/kg) or the $BMD_{10}$ [1] | |
|---|---|---|---|
| | | **RBC** | |
| | | **Males** | **Females** |
| MRID 48773401a | 1 day | 10% at 6.5 ($BMD_{10}$) | 10% at 14.9 ($BMD_{10}$) |
| MRID 48773401 (repeat CCA) | 11 days | 10% at 7.7 ($BMD_{10}$) | 10% at 8.7 ($BMD_{10}$) |
| MRID 45570601 (21-day oral) | 21 days | No inhibition | 10% at 9.9 ($BMD_{10}$) |
| MRID 43371201 (90-day oral) | 90 days | 10% at 61.6 ($BMD_{10}$) | 10% at 10.5 ($BMD_{10}$) |
| MRID 42980901 (chronic oral) | 365 days | No inhibition | 29% at 63 |
| | | **Brain** | |

| Table 4.3.2.1 – TCVP $BMD_{10}$ Results (mg/kg/day) for RBC and Brain AChE Inhibition Over Time in Adult Rats | | | |
|---|---|---|---|
| **MRID (study)** | **Days of Dosing** | **% inhibition at LOAEL (mg/kg) or the $BMD_{10}$ [1]** | |
| | | **Males** | **Females** |
| MRID 48773401a | 1 day | 10% at 7.4 ($BMD_{10}$) | 10% at 11.6 ($BMD_{10}$) |
| MRID 48294601 (acute CCA) | 1 day | 10% at 6.8 ($BMD_{10}$) | 10% at 11.3 ($BMD_{10}$) |
| MRID 48773401 (repeat CCA) | 11 days | 10% at 33.8 ($BMD_{10}$) | 10% at 7.2 ($BMD_{10}$) |
| MRID 45570601 (21-day oral) | 21 days | No inhibition | 10% at 14.7 ($BMD_{10}$) |
| MRID 43371201 (90-day oral) | 90 days | No inhibition | 12% at 6.7 |
| MRID 42980901 (chronic oral) | 365 days | No inhibition | 14% at 63 |

[1]The BMD, not the BMDL, estimates are shown when available in Table 4.3.2.1. According to the BMD guidance, the central estimate (i.e., the BMD) is used for purposes of comparison. The LOAEL and percent inhibition is presented when a BMD estimate is not available.

In adults, OPs generally exhibit a phenomenon known as steady state cholinesterase (AChE) inhibition. After repeated dosing at the same dose, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks; a pattern that is observed for most OPs, but not every OP, like TCVP, which shows no difference in response across duration. For TCVP, the results in Table 4.3.2.1 show a similar response across durations suggesting that steady state is reached after a single day of exposure. Further, TCVP exhibits a shallow dose-response curve for cholinesterase inhibition; *i.e.*, large increases in administered dose result in only small changes in AChE inhibition, although this may be attributed to differences in time after dosing that the cholinesterase measurements were made. This shallow dose response leads to variability in the AChE data and a relatively broad range of values of3.2 to 61.6 mg/kg/day for $BMD_{10}$s and 2.8 to 26.3 mg/kg/day for $BMDL_{10}$s (Appendix B). Given the results in Table 4.3.2.1 for TCVP, single day and steady state durations should have the same point of departure for human health risk assessment. As such, the endpoint selection for TCVP considers data available for all durations of dosing when choosing a protective POD.

## 4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for TCVP. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised

draft human health risk assessment ((D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al., 12/29/2014). Initially, the agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[8]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years. For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP)

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[8] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.-1; CDC, 2008)[9]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

**Table 4.4.1. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).**

| Pesticide | DMP | DMTP | DMDTP | DEP | DETP | DEDTP |
|---|---|---|---|---|---|---|
| Azinphos methyl | X | X | X | | | |
| Chlorethoxyphos | | | | X | X | |
| Chlorpyrifos | | | | X | X | |
| Chlorpyrifos methyl | X | X | | | | |
| Coumaphos | | | | X | X | |
| Dichlorvos (DDVP) | X | | | | | |
| Diazinon | | | | X | X | |
| Dicrotophos | X | | | | | |
| Dimethoate | X | X | X | | | |
| Disulfoton | | | | X | X | X |
| Ethion | | | | X | X | X |
| Fenitrothion | X | X | | | | |
| Fenthion | X | X | | | | |
| Isazaphos-methyl | X | X | | | | |
| Malathion | X | X | X | | | |
| Methidathion | X | X | X | | | |
| Methyl parathion | X | X | | | | |
| Naled | X | | | | | |
| Oxydemeton-methyl | X | X | | | | |
| Parathion | | | | X | X | |
| Phorate | | | | X | X | X |
| Phosmet | X | X | X | | | |
| Pirimiphos-methyl | X | X | | | | |
| Sulfotepp | | | | X | X | |
| Temephos | X | X | | | | |
| Terbufos | | | | X | X | X |
| Tetrachlorvinphos | X | | | | | |
| Trichlorfon | X | | | | | |

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

[9] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf



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For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al., 2008; Chen et al., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al., 2008; Chen et al., 2012; Racke et al., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al., 2008; Forsberg et al., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and Attention Deficit Hyperactivity Disorder (ADHD) were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] with additional support from a cross-sectional study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In

contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al. ,2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK-PD) model (D424485, D. Drew et al., 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[10] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children

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[10] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.



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who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increase in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the TCVP human health risk assessment, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

### 4.5 Safety Factor for Infants and Children (FQPA Safety Factor)

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety Factor will be retained for TCVP for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.** [11]

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[11] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

### 4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for TCVP is complete and includes developmental toxicity studies in the rat and rabbit, a reproductive toxicity study in the rat, acute and subchronic neurotoxicity studies in the rat, a developmental neurotoxicity study in the rat, a three component comparative cholinesterase study in the rat (acute, repeat, and gestational exposure), and an acute delayed hen neurotoxicity study.

As discussed in Section 4.5, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

### 4.5.2 Evidence of Neurotoxicity

TCVP is an organophosphate insecticide with an established neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used to derive points of departure (PODs). Neurotoxicity related to inhibition of AChE by TCVP, which was noted in the ACN and rabbit developmental toxicity studies, included transient clinical signs characteristic of cholinergic toxicity and tremors, as discussed above. The points of departure selected for this risk assessment are protective of these clinical signs.

### 4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The concern for susceptibility is low based on the lack of susceptibility following *in utero* exposure to TCVP in either the rat or rabbit developmental toxicity study or following *in utero* and/or pre-/post-natal exposure to TCVP in the 2-generation reproduction rat study. The apparent quantitative susceptibility observed in pups in the DNT occurred at the same dose level where 60% RBC and 45% brain cholinesterase inhibition occurred in pups and 62% RBC and 57% brain inhibition occurred in the adult females in the repeat CCA study. This comparison demonstrates that significant inhibition and toxicity also occurred in the maternal rat in the DNT, and repeat dosing showed no sensitivity with respect to the magnitude of the cholinesterase inhibition between the dam and pups. Furthermore, the effects observed in the DNT occurred at a dose 70-fold higher than the point of departure (POD). The POD is based on the AChE data from PND11 and PND21 pups from the acute CCA study, which provided the lowest POD, and is protective of the effects observed in the DNT.

As discussed in Section 4.5, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

### 4.5.4 Residual Uncertainty in the Exposure Database



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There are no residual uncertainties in the exposure database. The mostly refined dietary risk assessment uses food residues levels from monitoring data and from empirical studies, percent livestock treated data and model-estimated drinking water concentrations from maximum application rates. Residential exposure assessments use data from surrogate and chemical-specific sources. The exposure assumptions will not underestimate risks.

## 4.6 Toxicology Endpoint and Point of Departure Selections

### 4.6.1 Dose-Response Assessment

Table 4.6.4.1 summarizes the TCVP toxicity endpoints and points of departure (PODs) selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: For TCVP, there is no consistent pattern across studies, durations, lifestages, and routes. Following acute oral exposure, RBC and brain are equally affected, whereas the RBC compartment provided the lower BMDL estimate following repeat oral exposure in adults. Also, for each age group in the CCA studies, the magnitude of the RBC and brain inhibition is similar. Based upon the robustness of the AChE data and dose-response across the dose selection in the acute dose CCA rat study (see Appendix B for BMD analysis results), the RBC AChE data from PND 11 and 21 male and female pups were selected as the endpoint for deriving the acute and steady state POD for risk assessment.
- *Potentially susceptible populations (fetuses, juveniles, pregnant dams)*: The available AChE data across multiple lifestages (adults, pregnant females, fetuses, juveniles) show no quantitative sensitivity following repeat or acute exposure. The fetus is not more sensitive than the pregnant dam, and pregnant females were not more sensitive than non-pregnant females. There is also no consistent pattern with respect to sex difference. In the acute CCA, the adult male shows greater inhibition in both compartments than the adult female, whereas the adult female shows more inhibition (both compartments) in the repeat CCA and other repeat dose studies than the adult male.
- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with the exposure scenario(s) of interest. In the case of TCVP, there are single and repeat dose oral, repeat dose dermal, and repeat dose inhalation studies that contain measurements of RBC and brain AChE inhibition.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with the exposure duration of interest. In the case of TCVP, there are single day and steady state/repeat exposure oral studies and steady state dermal and inhalation studies. The oral AChE data show the magnitude of AChE inhibition does not significantly increase with time such that AChE inhibition from a single oral exposure is comparable to AChE inhibition after repeated oral exposure.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across



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studies. Based on a weight of evidence approach, the TCVP database allows for PODs to be derived from the most conservative BMDLs, which are consistent for the PND 11 and PND 21 rats in the acute CCA and adult animals in the acute and repeat CCA thereby increasing the confidence in such values.

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated $BMD_{10}$s and $BMDL_{10}$s. The $BMD_{10}$ is the estimated dose where AChE is inhibited by 10% compared to background AChE activity. The $BMDL_{10}$ is the lower confidence bound on the $BMD_{10}$ value. As a matter of science policy, the agency uses the BMDL, not the BMD, as the PoD (USEPA, 2012). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.4; an exponential model was used to fit the data. Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix A of this document, which includes an additional acute CCA identified since the last risk assessment. Summary tables of BMD analyses can be found in Appendix B and the technical details of the analysis can be found in the BMD memo (J. Bever; TXR No. 0056970; D420286).

*Acute Dietary (All Populations)*

A POD for the acute dietary (all populations) exposure scenario was derived from the results of the high quality, well-conducted acute dose CCA study (MRID 448773401a) in juvenile rats. Numerous estimates informed the $BMDL_{10}$ of 2.8 mg/kg/day, which was associated with RBC AChE inhibition in PND11 and PND 21 male and female juvenile rats and was therefore selected as the POD for the acute dietary exposure scenario for all populations. The lowest corresponding $BMD_{10}$ was 3.2 mg/kg/day. Data from the young rat from the acute CCA study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations.

The FQPA SF (10X) will be retained for infants, children, youths, and women of childbearing age due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5). The acute population adjusted dose (aPAD) for these lifestages is 0.0028 mg/kg/day (includes a total uncertainty factor of 1000X: 10X to account for interspecies extrapolation and 10X for intraspecies variation and the 10X FQPA SF). The only population subgroup for dietary exposure scenarios for which the FQPA SF is not retained is adults 50-99 years of age; therefore, the aPAD for this population subgroup is 0.028 mg/kg/day.

*Steady-State Dietary (All Populations)*

A POD for the steady-state dietary (all populations) exposure scenarios was derived from the same acute dose CCA study used for the acute dietary. A $BMDL_{10}$ of 2.8 mg/kg/day associated with RBC cholinesterase inhibition in male and female PND 11 and 21 rats was selected as a suitable POD for the steady-state dietary exposure scenario. The lowest corresponding $BMD_{10}$ was 3.2 mg/kg/day. Although the steady state dietary endpoint was selected from an acute dose comparative cholinesterase study, the duration of this study is considered appropriate for this exposure scenario since AChE data across the TCVP database demonstrate that there is no

progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose. A longer-term exposure does not result in a lower POD, as evidenced by the larger $BMD_{10}$s found for the repeat dose CCA data.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) is applied to the $BMDL_{10}$ to obtain an ssPAD of 0.0028 mg/kg/day for exposure scenarios with infants, children, youth, and women of child-bearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the ssPAD for this population subgroup is 0.028 mg/kg/day.

*Incidental Oral, Steady State*

For the purpose of assessing potential risk associated with incidental oral exposure from steady state durations, OPP selected the same POD (2.8 mg/kg/day) and endpoint as selected above for dietary exposure.

A total uncertainty factor of 1000X is appropriate for incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)). The Level of Concern (LOC) for incidental oral exposures is 1000.

*Dermal, Steady State*

No quantification of dermal non-cancer risk is required for TCVP since there were: (1) no treatment related effects (no clinical signs) at doses up to and including the limit dose of 1000 mg/kg/day in the dermal toxicity study; (2) both RBC and brain cholinesterase activity were assessed in the dermal study and neither compartment was affected at the limit dose; (3) there is no concern for quantitative susceptibility for juvenile or gestational lifestages based on results of the developmental, reproductive, or CCA toxicity studies.

*Inhalation, Steady State*

The steady state inhalation POD was selected from a 4-week inhalation toxicity study (MRID 48803501) in rats, based on an increase in RBC cholinesterase inhibition in both sexes. Females had slightly higher modeled values ($BMDL_{10}$ of 0.022 mg/L/day: $BMD_{10}$ of 0.12 mg/L/day) than males. The duration of this study is considered appropriate for the steady state exposure scenario since steady state occurs within 21 days, as demonstrated for other OPs, and a longer-term exposure would not be expected to result in a lower POD. The methods and dosimetry equations described in the agency's reference concentration (RfC) guidance are suited for calculating human equivalent concentrations (HECs) based on the inhalation toxicity POD obtained in rats exposed for 6 hours/day for an average of 5.5 days/week. The regional deposited dose ratio (RDDR), which accounts for the particulate diameter (mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD] of aerosols) can be used to estimate the different dose fractions deposited along the respiratory tract surface areas. Thus, the RDDR can

be used to adjust an observed inhalation particulate exposure of an animal to the predicted inhalation exposure for a human. For the subchronic inhalation toxicity study with TCVP, an RDDR of 2.525 was estimated based on extrarespiratory effects (RBC cholinesterase inhibition) in Sprague Dawley rats (bodyweight = 267g). The MMAD and GSD of 2.57 and 3.785 µm, respectively, at 0.05 mg/L were used to derive the RDDR.

The HECs are summarized in Table 4.6.4.3, as well as human equivalent doses (HEDs) calculated for residential and occupational handler scenarios. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

A total uncertainty factor of 300X is appropriate for inhalation exposures (3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments or a 10X database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)).

### 4.6.2 Recommendations for Combining Routes of Exposure for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major routes (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the oral, dermal, and inhalation routes are all derived from RBC cholinesterase inhibition. Thus, all routes can be combined.

### 4.6.3 Cancer Classification and Risk Assessment Recommendation

TCVP is classified as a Group C, possible human carcinogen, based on statistically significant increases in combined hepatocellular adenoma/carcinoma (primarily carcinomas) in the female B6C3F1 mouse, suggestive evidence of thyroid c-cell adenomas, and adrenal pheochromocytomas in the rat, as well as mutagenicity concerns. Following a reassessment of the mutagenicity data available on TCVP, it was determined that the relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[12]. A cancer potency factor ($Q_1{}^*$) of $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$ was estimated using the Weibull 83 time-to-tumor model. A 3/4 body weight scaling factor was used to convert from mouse to human equivalents. Following the submission and review of the required assays, the need for an updated cancer assessment will be determined.

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[12] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.



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### 4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

See Tables 4.6.4.1, 4.6.4.2, and 4.6.4.3 below.



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| Table 4.6.4.1. Summary of Toxicological Doses and Endpoints for TCVP for Use in Dietary and Non-Occupational Human Health Risk Assessments | | | | |
|---|---|---|---|---|
| **Exposure/ Scenario** | **Point of Departure** | **Uncertainty Factors*** | **Level of Concern for Risk Assessment** | **Study and Toxicological Effects** |
| Acute Dietary (all populations, except adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Acute RfD = 0.028 mg/kg/day<br>aPAD = 0.0028 mg/kg/day | Acute dose CCA study (MRID 48773401a) – Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND11 and 21 male and female RBC AChE inhibition |
| Acute Dietary (Adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 1x | Acute RfD = 0.028 mg/kg/day<br>aPAD = 0.028 mg/kg/day | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Steady State Dietary (all populations, except adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Steady State RfD = 0.028 mg/kg/day<br>ssPAD = 0.0028 mg/kg/day | Acute dose CCA study (MRID 48773401a) – Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Steady State Dietary (Adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 1x | Steady State RfD = 0.028 mg/kg/day<br>ssPAD = 0.028 mg/kg/day | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Incidental Oral (steady state) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Residential LOC for MOE = 1000 | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Dermal (steady state) | No potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day and no concern for quantitative susceptibility. | | | |

| | | | | |
|---|---|---|---|---|
| Inhalation (steady state) | $BMDL_{10}$=0.022 mg/L/day (males) | $UF_A$= 3x<br>$UF_H$=10x<br>FQPA SF = 10X | Residential LOC for MOE = 300 | Subchronic Inhalation Toxicity Study (MRID 48803501) – Rat<br><br>$BMD_{10}$ = 0.12 mg/L/day, based on RBC AChE inhibition in both sexes |
| Cancer (oral, dermal, inhalation) | Classification: A possible human (Group C) carcinogen. $Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$ | | | |

[1] **Explanation of Abbreviations:** Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies); MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. AChE = acetylcholinesterase. $BMDL_{10}$= benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute. ss = steady state or maximal AChE inhibition.

*The 10X FQPA SF is retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 for which the FQPA SF has been reduced to 1X.

**Table 4.6.4.2 Summary of Toxicological Doses and Endpoints for TCVP for Use in Occupational Human Health Risk Assessments**

| Exposure/ Scenario | Point of Departure | Uncertainty Factors | Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Dermal (steady state) | No potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day and no concern for quantitative susceptibility. | | | |
| Inhalation (steady state) | $BMDL_{10}$=0.022 mg/L/day (males) | $UF_A$= 3x<br>$UF_H$=10x<br>$UF_{DB}$= $10x^A$ | Occupational LOC for MOE = 300 | Subchronic Inhalation Toxicity Study (MRID 48803501) - Rat<br><br>$BMD_{10}$ = 0.12 mg/L/day, based on RBC AChE inhibition in both sexes |
| Cancer (oral, dermal, inhalation) | Classification: A possible human (Group C) carcinogen. $Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$ | | | |

[1] **Explanation of Abbreviations:** Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UFA = extrapolation from animal to human (interspecies). UFH = potential variation in sensitivity among members of the human population (intraspecies); $UF_{DB}$ = database uncertainty factor; MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$= benchmark dose lower limit for 10% response. AChE = acetylcholinesterase. SS = steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted

for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations including chronic.
[A] The 10X database uncertainty factor applies to occupational worker assessment to account for potentially pregnant workers due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

**Table 4.6.4.3 Summary of HEC/HED Values for TCVP**

| Population | Scenario | Tox Duration Adjustment | | HEC | | HED |
|---|---|---|---|---|---|---|
| | | hours/day[a] | days/week[b] | mg/L | mg/m$^3$ | mg/kg/day |
| Occupational | Handler | 0.75 | 1 | 0.042 | 41.663 | 3.94 |
| Residential | Handler | | | 0.056 | 55.550 | 1.31 |
| | Bystander | 0.25 | 0.714 | 0.010 | 9.920 | |

HEC = human-equivalent concentration; HED = human-equivalent dose. See Appendix C for details.
HEC = rat POD × daily duration adjustment × weekly daily duration adjustment × RDDR.
HED = HEC × human-specific conversion factor (11.8 L/hr/kg) × daily duration.
[a] hours of exposure [animal study (6 hours) ÷ human worker (8 hours) or bystander (24 hours)]
[b] days of exposure [animal study (5 days/week ÷ bystander (7 days/week)/human worker (5 days/week)]

## 4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for TCVP, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), TCVP is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[13] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. TCVP is on List 1 for which EPA has received all the required Tier 1 assay data. The agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[14].

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Animal Metabolism Studies

Residue Chemistry Memo: DP# 243528, 3/11/98, D. Miller
Residue Chemistry Memo: DP# 206721, 9/21/94, D. Miller (Addendum to RED)
Residue Chemistry Chapter to Tetrachlorvinphos RED (DP# 199644, 7/6/94, F. Suhre)
Residue Chemistry Memo: J. Abbotts, No DP#, 4/93, Results of Metabolism Committee Meeting

There are no registrations or tolerances for plant commodities, so plant metabolism studies are not required for TCVP. The qualitative nature of the residue in ruminants following oral or dermal dosing, and in poultry following dermal application, is adequately understood based on previously submitted studies. The HED Metabolism Committee (9/8/93 Meeting) has determined that the residues of concern for tolerance enforcement and for risk assessment for carcinogenicity are the parent compound and four metabolites: tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. For the non-cancer risk assessment for cholinesterase inhibition, tetrachlorvinphos is the only residue of concern.

#### 5.1.2 Summary of Environmental Degradation

Drinking Water Assessment Memo (EFED): DP# 419448, 11/6/14, C. Peck[15]

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[13] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of
chemicals.
[14] http://www.epa.gov/endo/
[15] C. Peck, 11/6/2014, D419448, Tetrachlorvinphos (TCVP) Drinking Water Assessment for Registration Review



ED_002155B_00027906-00040

TCVP is moderately mobile in soil and not stable in terrestrial or aquatic environments. The TCVP degradates appear to be as mobile, and in most cases more mobile, than the parent. TCVP is soluble in water at up to 11.6 mg/L, and is not expected to volatilize significantly due to a low vapor pressure of 2.6 x $10^{-7}$ torr (25°C). The compound is hydrophobic (Log $K_{ow}$ of 3.53). TCVP hydrolyzes in water at a pH-dependent rate. Hydrolysis is relatively rapid in alkaline water (half-life of 10.3 days at pH 9). In neutral to acidic water (pH 5 to 7), TCVP hydrolyzes with slower half-lives of 30 to 57 days. A major degradate of hydrolysis found in the aqueous solution at pH 9 was des-O-methyl tetrachlorvinphos (28% at Day 21). Hydrolysis rates for the TCVP Total Residue of Concern (TRC) could not be calculated, as not all degradates in the study extracts were identified; therefore, TCVP TRC was considered stable to hydrolysis.

TCVP isomer mixture (50:50, Z:E) readily biodegraded in aerobic soils, with a half-life of approximately 9 days. However, the rate of biodegradation for the mixed isomer of the parent TCVP was slightly reduced as concentrations decreased, which may indicate that one isomer degrades more rapidly than the other. Major soil degradates include TCPEol, TCCEol, TCPEone and TCBA. The TCVP TRC that were identified in the aerobic soils biodegraded with half-lives of from 53 to 200 days.

### 5.1.3 Comparison of Metabolic Pathways

Metabolism in ruminants (dermal and oral administration; tissue), poultry (oral; tissue) and rats (oral; excreta) is similar, generally resulting in parent TCVP and the four metabolites of concern (TCVPdeme, TCPEdiol, TCPEone and TCPEol). However, the metabolite TCPEone was not found in detectable levels in the rat metabolism study and the metabolite TCPEdiol was not detected in the goat studies. Unchanged parent TCVP was found in the goat dermal study, but was not detected in the goat oral study.

### 5.1.4 Residues of Concern Summary and Rationale

The HED Metabolism Committee (9/8/93 Meeting) has determined that the total residues of concern (TRC) for carcinogenicity are the parent compound tetrachlorvinphos and metabolites which, like tetrachlorvinphos, contain the 2,4,5 trichlorobenzene ring. For livestock commodities, the total residues of concern for carcinogenicity are tetrachlorvinphos [TCVP] plus the following four metabolites: des-O-methyl tetrachlorvinphos [TCVPdeme]; 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms) [TCPEol]; 2,4,5-trichloroacetophenone [TCPEone]; and 1-(2,4,5-trichlorophenyl)ethanediol [TCPEdiol]. For drinking water carcinogenicity assessment, the total residues of concern include the four aforementioned metabolites for livestock plus 2 additional degradates: 1-(2,4,5-trichlorophenyl)-2-chloroethanol [TCCEol], and 2,4,5-trichlorobenzoic acid [TCBA].

For the non-cancer risk assessment for cholinesterase inhibition, TCVP is the only residue of concern. For tolerance enforcement the residues of concern include TCVP plus, TCVPdeme, TCPEdiol, TCPEone and TCPEol.

See Appendix E for a table of parent and metabolite structures and chemical properties.

| Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression | | | | |
|---|---|---|---|---|
| **Matrix** | | **Residues included in Risk Assessment (Cholinesterase Inhibition)** | **Residues included in Risk Assessment (Carcinogenicity)** | **Residues included in Tolerance Expression** |
| Plants | Primary Crop | NA | NA | NA |
| | Rotational Crop | NA | NA | NA |
| Livestock | Ruminant | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol |
| | Poultry | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol |
| Drinking Water | | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol, TCCEol, TCBA | NA |

NA= not applicable
TCVP= tetrachlorvinphos
TCVPdeme,= des-O-methyl tetrachlorvinphos
TCPEol= 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms)
TCPEone= 2,4,5-trichloroacetophenone
TCPEdiol= 1-(2,4,5-trichlorophenyl)ethanediol
TCCEol =l-(2,4,5-trichlorophenyl)-2-chloroethanol
TCBA =2,4,5-Trichlorobenzoic acid

## 5.2 Residue Chemistry and Food Residue Profile

Residue Chemistry Memo: D243528, 3/11/98, D. Miller

*Residue Chemistry*

Tolerances are established for residues of TCVP in animal commodities since residues may occur in milk, eggs, meat, fat, or meat byproducts as a result of the registered uses on livestock (oral and dermal uses) and around livestock premises. There are no registered uses on plant (including feedstuffs) commodities. This section provides the background and current status of residue chemistry requirements for TCVP and includes residue data submitted and reviewed since the 1994 Residue Chemistry Chapter of the TCVP RED and the 2006 TCVP RED.

The 1994 Residue Chemistry Chapter cited the need for the following magnitude of the residue studies: *New magnitude of the residue studies reflecting oral and dermal exposure of beef cattle, dairy cattle, and hogs, and dermal exposure of poultry to tetrachlorvinphos are required. All residues of concern should be analyzed in cattle, hogs, and poultry using validated analytical methods.*

Subsequent to the TCVP RED, in 2007, residue studies on cattle (dermal and oral treatments; MRID 47193001) and poultry (dermal treatment; MRID 47193001) were submitted, as was a companion storage stability study (MRID 47193001) and a residue analytical method (MRID 47369201). Those studies were reviewed under DP #s D320848, D320858, D320859, and D381350 (C. Olinger, 10/7/10, *Tetrachlorvinphos. Cattle Oral/Dermal and Poultry Dermal Studies. Summary of Residue Data Submitted in Support of Reregistration*). The submitted magnitude of the residue studies on cattle and poultry were determined to be inadequate, but upgradeable pending submission of supporting storage stability data. The companion storage stability study was determined to be unacceptable because of study design. Additional information was also requested regarding the maximum storage duration of all samples collected from both the cattle and poultry studies. In 2011, additional information (MRIDs 486378101 and 48319001) pertaining to the storage stability deficiencies was submitted and reviewed (C. Olinger, 3/25/11, D385359 and D386954, *Tetrachlorvinphos. Response to Comment on Storage Stability Residue Data Deficiencies)*. The poultry and cattle residue data (860.1480) deficiencies are now fulfilled and no further data are being required.

In response to the data requirement for a residue study in hogs, a waiver request was submitted and granted in 2011 (C. Olinger, 4/25/11, D320857, *Tetrachlorvinphos. Request for Waiver of a Swine Magnitude of Residue Study).* It was determined that TCVP residues in swine tissues are not likely to be higher than the residues in ruminants and that ruminant data may be translated to swine. The conclusion was based on the poor oral and dermal absorption of TCVP in livestock and the fact that residence time in swine intestines is significantly shorter relative to that in a ruminant. No additional residue data (860.1480) on hogs are being required.

In response to a TCVP Generic Data Call-In (GDCI) issued 12/29/09, data were submitted evaluating TCVP metabolites using the FDA Multiresidue Methods Test guidelines in Pesticide Analytical Manual (PAM) Vol. I (MRID 48655201) and were reviewed 7/5/12 (D. Drew, D396833, *Tetrachlorvinphos (TCVP). Multiresidue Methods (MRM) Study of the Metabolites of TCVP*). The data requirement for MRM testing (860.1360) has been fulfilled.

The registrant submitted a proposed method SCR/006 for tolerance enforcement of livestock commodities that includes detection of TCVP and the metabolites TCVPdeme, TCPEol, TCPEone and TCPEdiol (MRID 47369201, 2007). The HED review (D320848, D320858, D320859, and D381350) determined that the method was adequate, but that an independent laboratory validation (ILV) trial remained outstanding. A Generic Data Call-In (GDCI) for an ILV was originally issued December 29, 2009. A different proposed method (Method 14020.6106) and an associated ILV study (Method 14020.6107) were subsequently submitted to the agency (MRID 49419301, 2015). Because the proposed Method 14020.6106 monitors only a single ion transition for each analyte, alternative confirmatory procedures are necessary; the previously submitted method SCR/006 (MRID 47369201) is considered acceptable as a confirmatory method. The analytical method test data for 14020.6106 are classified as scientifically acceptable for use as an analytical method for ruminant and poultry commodities.

*Food Residue Profile*

The available magnitude of the residue study for dairy cattle reflect a combination of two treatments: oral administration of tetrachlorvinphos for 29-31 days at actual rates of 1.51-1.55 and 4.63 g ai/750 kg BW per day (6.3-6.5x and 19.3x, respectively, the maximum registered rate of 0.24 g ai/750 kg BW for feed-through treatment) and dermal spray treatments on three occasions, at ~14 day intervals, at actual rates of 10.11 and 19.2-19.5 g ai per animal per dose (~0.5 and 1.0x, respectively, the maximum registered rate of 18.9 g ai/animal for direct animal spray treatment). At the combined treatment regime (6.5x dermal spray plus 1x oral treatment), the maximum total residues of concern (with the maximum residues of the parent in parentheses) were: 0.072 (0.036) ppm for milk, 0.078 (<0.01) ppm for cream, 0.158 (<0.01) ppm for liver, 0.278 (0.015) ppm for kidney, 0.272 (0.212) ppm for muscle, 0.842 (0.558) ppm for subcutaneous fat, and 0.747 (0.340) ppm for peritoneal fat.

The available magnitude of the residue study for poultry reflects 6-7 dermal spray treatments of laying hens with an EC formulation, made at two-week retreatment intervals, at 0.0908, 0.182, or 0.545 g ai/hen/application. These application rates, respectively, correspond to ~0.5x, 1.0x, or 2.9x the maximum registered direct spray treatment rate of 0.19 g ai/bird daily. At ~1.0x, the maximum total residues of concern (with the maximum residues of the parent in parentheses) were: 0.288 (0.026) ppm for egg, 0.517 (0.016) ppm for liver, 0.583 (0.022) ppm for kidney, 0.396 (0.082) ppm for muscle, 19.405 (6.030) ppm for skin with fat, and 1.298 (0.099) ppm for abdominal fat.

There were no detectable residues of parent TCVP in the most recent USDA PDP monitoring data for beef meat, liver, or fat, or for milk and cream; nor were there detectable residues in pork fat. There were no detectable residues in chicken meat or liver. There was one detectable residue in egg just above the method limit of detection (LOD; 742 samples). PDP did not analyze chicken fat or skin for TCVP. The TCVP metabolites of concern for cancer assessment were not measured by PDP.

## 5.3 Water Residue Profile

Drinking Water Assessment Memo (EFED): D419448, 11/6/14, C. Peck

The Surface Water Concentration Calculator (SWCC) computer model was used to generate surface water Estimated Drinking Water Concentrations (EDWCs) for use in the human health dietary risk assessment, while the PRZM-GW and SCI-GROW models were used to generate groundwater EDWCs. The residues of concern for acute and steady state dietary exposure included cholinesterase-inhibiting compounds, which were determined to be TCVP parent only. For carcinogenicity, (total) residues of concern (TRC) included TCVP and the following metabolites which, like TCVP, contain the 2,4,5 trichlorobenzene ring: des-O-methyl tetrachlorvinphos,1-(2,4,5-trichlorophenyl)ethanediol, TCPEol (1-(2,4,5-trichlorophenyl)ethanol), TCPEone (2,4,5-trichloroacetophenone), TCCEol (l-(2,4,5-trichlorophenyl)-2-chloroethanol), and TCBA (2,4,5-trichlorobenzoic acid).

Maximum EDWCs (based on maximum labeled usage for kennels, poultry droppings, garbage and manure piles, and corrals) for TCVP residues in surface water and groundwater for dietary assessment are presented in Table 5.3. Daily time series outputs for the thirty year simulation were also provided to HED for use in dietary exposure modeling.

This dietary assessment used the maximum total residues of concern (TRC) EDWC of 22.4 ug/L for the cancer analysis, input as a single point estimate. For the selected drinking water scenarios, a distribution of surface water residues was used probabilistically in the dietary model for non-cancer assessments based on cholinesterase inhibition. The following paragraph describes the derivation of those distributions.

Daily time-series outputs that simulate 29 years (1962-1990) of residues of TCVP in surface drinking water for the outdoor uses (on kennels, poultry droppings, garbage and manure piles, and corrals) were modeled using the SWCC. No further adjustments were made to the acute distribution files, but since the steady state average dietary assessments use 21-day forward rolling averages for drinking water, the steady state distributions were further adjusted to be 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc. The 21-day rolling average continues until the last 20 days of residues of the final distribution year.

**Table 5.3 Summary of Estimated Surface Water and Groundwater Concentrations for Tetrachlorvinphos**

| DRINKING WATER SOURCE (MODEL USED) | MAXIMUM ESTIMATED DRINKING WATER CONCENTRATION (EDWC) | |
|---|---|---|
| | Acute (µg/L) (TCVP only) | Cancer (µg/L) (TRC) |
| Surface water (SWCC) | **4.03** | 4.11 |
| Groundwater (PRZM-GW) | $8.54 \times 10^{-5}$ | **22.4** |
| Groundwater (SCI-GROW) | $5.61 \times 10^{-3}$ | $7.36 \times 10^{-2}$ |

* EDWCs based on maximum labeled usage for kennels, poultry droppings, garbage and manure piles, and corrals.

## 5.4 Dietary Risk Assessment

Dietary Assessment Memo: D436835, 9/20/2016, D. Drew[16]

[16] D. Drew, 9/20/2016, Tetrachlorvinphos (TCVP). Revised Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment, D436835.

The previous dietary risk assessment for tetrachlorvinphos was conducted on 10/29/2014 (D. Drew, D426985, *Tetrachlorvinphos (TCVP) Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment*). That assessment has been updated in D436835 (D. Drew, 9/20/2016, Tetrachlorvinphos (TCVP). *Revised Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment*) to reflect changes in the toxicological PODs for the acute and steady state dietary exposures. In addition, minor corrections have been made based on comments received on the 2014 dietary assessment (MRID 4989101, Bayer CropScience, *Comments to EPA's "Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment for Registration Review", Docket ID: EPA-HQ-OPP-2008-0316*).

### 5.4.1 Description of Residue Data Used in Dietary Assessment

HED has conducted acute, steady state, and cancer dietary (food and drinking water) exposure and risk assessments using DEEM version 3.16 for TCVP.

The dietary exposure analyses for TCVP are refined. The only food forms included in the analyses are based on animal commodities. The food residues were based upon U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) monitoring data except in a couple of instances where no appropriate PDP data were available (i.e., high-end residues from poultry dermal studies were used for poultry fat and poultry skin). The Biological and Economic Analysis Division (BEAD) of OPP provided percent livestock treated information. Model-derived estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effect Division (EFED). EDWCs were based on spot applications to kennels, poultry droppings, garbage and manure piles, and corrals and were directly incorporated into the assessments as described in Section 5.3 above.

Since the PDP only analyzed for residues of TCVP (and not for TCVP metabolites) a factor was applied to the PDP residues in order to account for all the metabolites of concern for the cancer assessment. The factor was calculated by determining the ratio of parent TCVP to total residues of concern in the livestock residue studies (see Table 2, D436835).

### 5.4.2 Percent Crop Treated Used in Dietary Assessment

For the acute and steady state analyses, the maximum estimated percent livestock treated of 3% was used for cattle and swine and the estimated maximum of 11% was used for poultry.

For the cancer analysis, the following estimated average percent livestock treated values were used: 1% for dairy cattle, 2% for beef cattle and swine, and 6% for poultry.

### 5.4.3 Acute Dietary Risk Assessment

The refined acute dietary (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 190% of the aPAD.

When drinking water is analyzed by itself, the acute dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95th and 99.9th percentile of exposure.

Most of the exposure from food is due to the high-end residue on chicken skin from poultry dermal studies (residue on uncooked chicken skin from direct dermal spray applications at maximum labeled rates with a 0-day pre-slaughter interval).

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

**Table 5.4.3.1. Results of Acute Dietary (Food Only) Exposure and Risk Analysis.**

| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.0028 | 0.000022 | < 1 | 0.000680 | 24 | 0.002806 | 100 |
| All Infants (<1 year old) | 0.0028 | 0.000012 | < 1 | 0.000288 | 10 | 0.002739 | 98 |
| Children 1-2 years old | 0.0028 | 0.000069 | 2.5 | 0.001073 | 38 | 0.004708 | 170 |
| **Children 3-5 years old** | 0.0028 | 0.000054 | 1.9 | 0.001386 | 50 | 0.005230 | 190 |
| Children 6-12 years old | 0.0028 | 0.000037 | 1.3 | 0.000938 | 33 | 0.003941 | 140 |
| Youth 13-19 years old | 0.0028 | 0.000024 | < 1 | 0.000731 | 26 | 0.003318 | 120 |
| Adults 20-49 years old | 0.0028 | 0.000022 | < 1 | 0.000722 | 26 | 0.002584 | 92 |
| Adults 50-99 years old | 0.028 | 0.000011 | < 1 | 0.000492 | 1.8 | 0.001690 | 6.0 |
| Females 13-49 years old | 0.0028 | 0.000020 | < 1 | 0.000651 | 23 | 0.002300 | 82 |

[1] Population with the greatest exposure is in bold.
[2] aPAD = acute population-adjusted dose.

**Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only) Exposure and Risk Analysis.**

| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000121 | 4.3 |
| **All Infants (<1 year old)** | 0.0028 | 0.000022 | < 1 | 0.000093 | 3.3 | 0.000369 | 13 |
| Children 1-2 years old | 0.0028 | 0.000012 | < 1 | 0.000048 | 1.7 | 0.000187 | 6.7 |

| Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| Children 3-5 years old | 0.0028 | 0.000011 | < 1 | 0.000041 | 1.4 | 0.000147 | 5.2 |
| Children 6-12 years old | 0.0028 | 0.000008 | < 1 | 0.000030 | 1.1 | 0.000111 | 4.0 |
| Youth 13-19 years old | 0.0028 | 0.000006 | < 1 | 0.000025 | < 1 | 0.000095 | 3.4 |
| Adults 20-49 years old | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000118 | 4.2 |
| Adults 50-99 years old | 0.028 | 0.000009 | < 1 | 0.000032 | < 1 | 0.000110 | < 1 |
| Females 13-49 years old | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000120 | 4.3 |

[1] Population with the greatest exposure is in bold.
[2] aPAD = acute population-adjusted dose.

### 5.4.4 Steady State Dietary Risk Assessment

The refined steady state (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the steady state population adjusted dose (ssPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 120% of the ssPAD.

The steady state dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95th and 99.9th percentile of exposure.

Most of the exposure from food is due to the high-end residue on chicken skin from poultry dermal studies (residue on uncooked chicken skin from direct dermal spray applications at maximum labeled rates with a 0-day pre-slaughter interval).

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

| Table 5.4.4.1. Results of Steady State Dietary (Food Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| General U.S. Population | 0.0028 | 0.000092 | 3.3 | 0.000599 | 21 | 0.001994 | 71 |
| All Infants (<1 year old) | 0.0028 | 0.000020 | < 1 | 0.000299 | 11 | 0.001843 | 66 |
| Children 1-2 years old | 0.0028 | 0.000128 | 4.6 | 0.001070 | 38 | 0.003181 | 110 |
| **Children 3-5 years old** | 0.0028 | 0.000152 | 5.4 | 0.001214 | **43** | **0.003444** | **120** |
| Children 6-12 years old | 0.0028 | 0.000130 | 4.6 | 0.000782 | 28 | 0.002991 | 110 |
| Youth 13-19 years old | 0.0028 | 0.000116 | 4.1 | 0.000645 | 23 | 0.002118 | 76 |
| Adults 20-49 years old | 0.0028 | 0.000112 | 4.0 | 0.000621 | 22 | 0.001971 | 70 |

| Table 5.4.4.1. Results of Steady State Dietary (Food Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| Adults 50-99 years old | 0.028 | 0.000049 | < 1 | 0.000418 | 1.5 | 0.001105 | 3.9 |
| Females 13-49 years old | 0.0028 | 0.000098 | 3.5 | 0.000572 | 20 | 0.001481 | 53 |

[1] Population with the greatest exposure is in bold.
[2] ssPAD = steady state population-adjusted dose.

| Table 5.4.4.2. Results of Steady State Dietary (Drinking Water Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| General U.S. Population | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000096 | 3.4 |
| **All Infants (<1 year old)** | 0.0028 | 0.000024 | < 1 | 0.000088 | 3.2 | 0.000300 | 11 |
| Children 1-2 years old | 0.0028 | 0.000013 | < 1 | 0.000045 | 1.6 | 0.000143 | 5.1 |
| Children 3-5 years old | 0.0028 | 0.000011 | < 1 | 0.000038 | 1.4 | 0.000114 | 4.1 |
| Children 6-12 years old | 0.0028 | 0.000008 | < 1 | 0.000028 | < 1 | 0.000085 | 3.0 |
| Youth 13-19 years old | 0.0028 | 0.000007 | < 1 | 0.000023 | < 1 | 0.000075 | 2.7 |
| Adults 20-49 years old | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000094 | 3.4 |
| Adults 50-99 years old | 0.028 | 0.000009 | < 1 | 0.000030 | < 1 | 0.000087 | < 1 |
| Females 13-49 years old | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000095 | 3.4 |

[1] Population with the greatest exposure is in bold.
[2] ssPAD = steady state population-adjusted dose.

### 5.4.5 Cancer Dietary Risk Assessment

The refined cancer dietary (food and drinking water) assessment resulted in an estimated exposure to TCVP and its metabolites containing the 2,4,5 trichlorobenzene moiety (the residues of concern for cancer) of 0.000513 mg/kg/day. Applying the $Q_1$* of 0.00183 $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of $9 \times 10^{-7}$. Drinking water is the major contributor to the cancer dietary risk estimate.

| Table 5.4.5.1. Summary of CANCER Dietary Exposure and Risk for Tetrachlorvinphos (and metabolites). | | | | | | |
|---|---|---|---|---|---|---|
| Population Subgroup | Food and Water | | Food Only | | Water Only | |
| | Exposure (mg/kg/day) | Risk | Exposure (mg/kg/day) | Risk | Exposure (mg/kg/day) | Risk |
| Adults | 0.000513 | $9 \times 10^{-7}$ | 0.000044 | $8 \times 10^{-8}$ | 0.000469 | $8 \times 10^{-7}$ |

## 6.0 Residential and Non-Occupational Exposure/Risk Characterization

Occupational and Residential Exposure Memo: D436833, 12/21/2016, W. Britton [17]

Residential exposures (handler and post-application) are anticipated from the use of TCVP pet products for dogs and cats including collars, dusts/powders, and pump/trigger sprays. Exposures are expected for adults who apply TCVP products to their pets and from post-application exposures for adults and children who may contact previously treated pets. Residential TCVP handler and post-application exposures are anticipated to be short- (1 to 30 days), intermediate- (1 to 6 months), and long-term (>6 months – *for pet collar scenarios only*). However, because of the steady state AChE inhibition exhibited by the OPs, steady state (typically 21 days and longer for OPs, but 1 day for TCVP) residential exposures were assessed for TCVP pet products.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

Following EPA's December 21, 2015 Draft TCVP risk assessment, Bayer HealthCare, Hartz Mountain Corporation, and NRDC submitted comments during the public comment period, primarily regarding the formulation type of pet collars. This document addresses, where appropriate, those comments. A comprehensive response to comments on the TCVP draft human health risk assessment (including ORE-specific comments) is also provided in the following memo: D. Drew et al., Tetrachlorvinphos (TCVP) Health Effects Division Response to Comments on the December 21, 2015 Draft Human Health Risk Assessment for TCVP Registration Review, D433403, 12/21/2016.

Formulation Type Issue: In 2009, the Natural Resources Defense Council (NRDC) petitioned the EPA to cancel all pet uses for the pesticide tetrachlorvinphos (TCVP). In 2014, the agency responded to the 2009 petition by conducting a human health risk assessment for all currently registered TCVP products which include collars, dusts/powders, and pump and trigger spray formulations. That risk assessment was dated Nov. 5, 2014. At that time, no human health risks of concern were identified for any TCVP pet product, and the petition to cancel all pet products was denied on Nov. 6, 2014. The NRDC subsequently responded to the agency's denial with arguments presented in NRDC's Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.) (Opening Brief). Among the arguments raised by NRDC was the assertion that the agency incorrectly considered the TCVP flea collar formulation to be a liquid formulated product:

*"NRDC states that the EPA failed to 'research' the TCVP flea collar label; instead it ignored the information in the label right on the box regarding the chemical formulation.' [NRDC Opening*

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[17] W. Britton *et al.*, 12/21/2016, D436833, Tetrachlorvinphos: Final Occupational and Residential Exposure Assessment for Registration Review

*Brief, p.67]. The label for the Hartz UltraGuard Flea and Tick Collar for Dogs (EPA Reg. No. 2596-84) states that 'as the collar begins to work, a fine white powder will appear on the surface.' As a result, NRDC argues that the transfer coefficient (TC) recommended for solid formulations should have been used instead of the transfer coefficent for liquid formulations as is recommended by the 2012 Residential SOPs."*[18]

The agency responded to this and all other arguments raised by NRDC in a December 21, 2015 memorandum,[19] issued along with the Draft risk assessment for Registration Review. The following is an excerpt of the agency's response relating to the pet collar formulation issue:

*"Per EPA's 2012 Residential SOPs*[20]*: Treated Pets, pet collar products are categorized as a liquid formulation. This position was based on research conducted at the time of SOP development that supported that pet collars function by means of diffusion, transferring from the collar to the surrounding area. More specifically, the active ingredient, which is embedded in the collar matrix, diffuses slowly through the matrix, thus controlling the amount of the active ingredient at the collar's surface. The active ingredient available on the surface of the pet collar then "rubs off" or transfers from the collar to the animal's hair coat via embedded lubricants which function as transfer agents at the surface of the collar. Based on the categorization of pet collars as liquid formulations, the assessment of post-application exposures for these product types would be conducted with use of the TCs, and the fraction active ingredient on the hands from TC studies ($Fai_{hands}$) recommended for the assessment of liquid formulated products as recommended in the 2012 Residential SOPs.*

*The information provided by NRDC states that the label for the Hartz UltraGuard Flea and Tick Collar for Dogs (EPA Reg. No. 2596-84) states that "as the collar begins to work, a fine white powder will appear on the surface." HED has confirmed that this statement is present on the current labeling for the identified product and that an identical statement is also found on the following TCVP pet collar products (5 of 9 total pet collar products): EPA Reg. Nos. 2596-62, 2596-63, 2596-83, 2596-84, and 2596-139. Taking label statements into account, and based upon further research which suggests that some pet collars may act by extrusion of the active ingredient from the collar matrix as a fine dust, HED has reconsidered the position that the TCVP pet collars are all liquid formulated products. As a result of this uncertainty, in the TCVP draft human health risk assessment in support of registration review, HED has updated the assessment of post-application risks from TCVP pet collars in consideration of both the dust- and liquid-specific TCs and $Fai_{hands}$ recommended SOP values."*[21]

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[18] W. Britton. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589, at 8 (summarizing NRDC's argument).

[19] *Id.*

[20] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[21] *Id.* at 8-9.

In response to the 2015 Draft TCVP risk assessment, Bayer HealthCare submitted comments to address the formulation type issue. Bayer agreed with the approach employed by the agency, stating: "*Based on the NRDC assertion and the statement on the collar packaging the agency has taken the understandable approach of calculating the post-application exposure, using both liquid and solid formulation transfer coefficients, until the uncertainty is resolved.*" Bayer proceeded to address the formulation type issue by describing how the active ingredient is released from the collar and distributed on the animal. Bayer described that, "*To achieve their goal of effective pest control, the flea collars are designed to deliver the insecticide from the collar in either a liquid or solid state. The collar is made from a mixture of plastic resins and resin modifiers. The resins are formulated to have appropriate strength and flexibility so the collar can withstand the shaping operations without cracking or crumbling. The resins must also have appropriate release characteristics, such that the TCVP (or other insecticide active ingredient) can escape the collar at the proper rate, while inert components remain in the collar.*"

Per Bayer, TCVP is distributed on the animal by abrasion or movement against the animal or diffusion from the animal's body heat. "*Within a few days after manufacture, the insecticide begins to migrate from within the body of the collar and form a coating of particles, resembling a dust or powder on the surface of the collar. As the particles of the active ingredient are displaced or shaken from the surface due to the normal activity of the animal, additional particles appear by migration from the body of the composition to replace the insecticide particles displaced from the surface (i.e., the displaced particles are replenished continuously). This describes the typical release mechanism and explains the presence of the powder as raised by NRDC. The powders are in the immediate vicinity of the collar; however, this is not necessarily the form in which the insecticide is dispersed to the animal or relevant to the transfer coefficient.*" They continued to describe that the sebaceous glands within the dog's skin that lubricate the hair are the mechanism for dispersion of the insecticide. "*Insecticides that are used in flea collars are lipophilic and soluble in the animal's skin oils. So, even though the collars may release some of the insecticides as a solid they are dispersed along the animal's body as a solution or suspension in the animal's skin via the natural skin oils.*" As such, the assessment of human health risks from TCVP pet collars were conducted in a manner that accounts for the likelihood of the presence of both liquid and solid forms while considering the isolated location (i.e., the head/neck) of ai in the dust/powder form.

While informative, Bayer's comments pose a dilemma for the agency. Although they describe the mechanism of dispersion of active ingredient along the animal's body as a solution or suspension in the skin, they also indicate that the insecticide begins to migrate from within the collar as a "coating of particles, resembling a dust or powder form on the surface of the collar" and that "flea collars are designed to deliver the insecticide from the collar in either a liquid or solid state." The mechanism of active ingredient dispersion via the skin alone is not adequate to describe the potential for post-application exposures. If the active ingredient is present as a liquid or particulate or dust on the surface of the pet collar, it could be transferred in either form from the collar to the pet's fur immediately surrounding and result in the potential for post-application exposures from either direct contact with the pet collar, or the surrounding fur.

Formulation Type Approach: A unique approach has been applied in order to account for the potential for exposures from the presence of TCVP to exist as both liquid and solid forms concurrently. The approach uses the same methodologies described in the 2012 Residential SOPs for assessment of residential handler and post-application exposure assessment for pet collar usage. However, whereas the 2012 Residential SOPs recommend that pet collars be assessed as a liquid formulation, the present approach assesses pet collar exposures as both a liquid and solid form. For residential handlers, this means use of the liquid UE data as recommended by the 2012 Residential SOPs and chemical-specific dust UE data for these formulation types. For the residential post-application exposure assessment, this means use of transfer coefficients (dermal exposures) and the fraction of active ingredient on hands from the transfer coefficent studies (hand-to-mouth exposures) specific to both liquid and solid formulation types.

The individual dust and liquid formulation handler and post-application doses were estimated, and then another step was included in the assessment where the liquid and dust doses were averaged assuming a ratio of liquid to dust in the collar formulation. For both handler and post-application scenarios, ratios of 1/99, 50/50, and 99/1 liquid/dust were assumed to cover a range of potential exposures.

The methodologies and inputs used for the individual formulation assessments for residential handlers and residential post-application exposures are described in Appendix B of the corresponding ORE memo (Memo, W. Britton *et al*, D436833).

Due to NRDC's argument related to the TCVP pet collar formulation, the agency has begun efforts to reevaluate pet collar formulation type to carefully consider whether pet collar products are more closely related to more traditional liquid formulation pet products such as shampoos and spot-ons, or solid formulated products such as dusts and powders. In following with this evaluation, the agency intends to request and review additional information relating to all registered pet collar products as they undergo registration review, as well as any proposed new pet collar uses. This evaluation will continue until the agency is satisfied that, based on the design and operation of pet collar products, a final formulation type decision can be made along with recommendations for human health risk assessment of exposures to pet collar-treated pets.

## 6.1 Residential Handler Exposures

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are assumed to complete all elements of an application without use of any protective equipment.

Residential handler exposures to TCVP pet products may occur via the dermal or inhalation routes while the product is placed on a cat or dog. Both steady state non-cancer and cancer residential handler exposure assessments were performed for adult homeowners applying TCVP pet collars, dusts/powders, and pump/trigger sprays products to cats and dogs. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are

assessed.

The exposure data and assumptions that underlie the residential handler non-cancer risk estimates can be referenced in the 2014 residential assessment[22] and the 2012 Residential SOPs. The algorithms used to estimate non-cancer exposure and dose for residential handlers can be found in Appendix B of the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833) and/or the 2012 Residential SOPs.[23]

Due to the uncertainty associated with whether TCVP pet collars are liquid and/or dust formulated products, residential handler steady state inhalation exposures for TCVP pet collar application were assessed (as described above in Section 6.0) assuming pet collars could be liquid and solid (dust) formulations concurrently, with varying ratios liquid/dust. When assuming the TCVP pet collars are a liquid formulation, the liquid-specific unit exposures (UE) values (i.e., surrogate data from a spot-on applicator study) from the 2012 Residential SOPs were used. When assuming the pet collars are a solid formulation, HED used the best available data, a TCVP dust/powder applicator exposure study (MRID 45519601).

The liquid formulation spot-on surrogate UE data assumes negligible inhalation exposure; therefore, only the dust-specific UE data (i.e., a TCVP dust/powder applicator exposure study) is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates

*Pet Collars:* Because there is uncertainty whether the TCVP pet collars are liquid and/or dust formulated products, residential handler (adults) steady state inhalation exposures were evaluated assuming both liquid and solid (dust) formulations are present concurrently with varying ratios of liquid/dust. No inhalation risks of concern were identified for residential handlers for any liquid/dust formulation ratio assumption. When assuming a ratio of 1/99 liquid/dust, MOEs range from 920 to 4,600; when assuming a ratio of 50/50 liquid/dust, MOEs range from 1,800 to 9,100; and when assuming a ratio of 99/1 liquid/dust, MOEs range from 91,000 to 450,000 (LOC = 300).

*Dust/Powder and Pump/Trigger Spray*: All residential handler (adults) non-cancer steady state inhalation risks estimated for the TCVP pet dust/powder pump/trigger spray formulations are not of concern (i.e., all MOEs are > 300; LOC = 300; range = 3,200 to 160,000).

A summary of residential handler exposures and risks is presented in Appendix G.

Residential Handler Cancer Exposure and Risk Estimate Equations

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[22] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

[23] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a Lifetime Average Daily Dose (LADD) is first calculated and then compared with a $Q_1$* that has been calculated for TCVP based on dose response data in the appropriate toxicology study ($Q_1$* = 1.83 x $10^{-3}$ (mg/kg/day)$^{-1}$). Absorbed average daily dose (ADD) levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the $Q_1$* to obtain cancer risk estimates.

The exposure data and assumptions that underlie the residential handler cancer risk estimates can be found in the 2014 residential assessment[24] and the 2012 Residential SOPs. The algorithms used to estimate the LADD and cancer risk for residential handlers can be found in Appendix B of the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833).

Summary of Residential Handler Cancer Exposure and Risk Estimates

*Pet Collars:* Residential handler cancer risks (combined dermal and inhalation) estimated for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio are all $10^{-7}$. When assuming a 50/50 liquid/dust formulation ratio (use of liquid-specific and dust-specific UE data) are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$.

*Dust/Powder and Pump/Trigger Spray*: Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$.

A summary of residential handler cancer exposures and risks is presented in Appendix H.

## 6.2 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of contacting a cat/dog previously treated with TCVP pet products (dusts/powders, pump/trigger sprays, pet collars). The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenario:

1) Post-application incidental oral (hand-to-mouth) exposure (children 1 to < 2 years olds only) from contacting cats and dogs treated with TCVP.

Since there is no non-cancer dermal hazard for TCVP, a quantitative non-cancer post-application dermal exposure assessment was not performed for adults or children. A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from applications to pets.

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[24] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

The lifestages selected for each post-application scenario (i.e., children 1 to < 2 years old) are based on an analysis provided as an Appendix in the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833) and the 2012 Residential SOPs.[25] While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Non-Cancer Post-Application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential non-cancer post-application risk assessment. The exposure data and assumptions that underlie the residential non-cancer post-application risk estimates can be found in the 2014 residential assessment[26] and the 2012 Residential SOPs.

Several inputs and assumptions that underlie the residential post-application risk assessment of TCVP pet products were addressed previously by EPA in the responses to NRDC's August 5, 2015 Opening Brief,[27] including: the use of the Davis study; TCVP pet collar product formulation type; daily exposure time spent in contact with TCVP treated pets; indirect hand-to-mouth activity; and the application of transferable residue data in EPA's risk assessment algorithms. NRDC has repeated all of these same arguments in its comments submitted for the 2015 DRA. EPA has addressed the use of the Davis study and TCVP pet collar product formulation type arguments herein. The agency's responses to all other arguments remain the same as addressed previously.

*Residue Transfer Assumptions:* Chemical-specific residue transfer studies were used for assessment of post-application exposures from registered TCVP pet products.

*Dust/Powder and Pump/Trigger Spray:* Consistent with the 2015 draft ORE assessment for Registration Review, a TCVP powder and pump spray study (MRID 45485501) was used to assess post-application exposure for these scenarios. A summary and discussion of the use of these data was included in the 2014 residential risk assessment. As described in the 2014 residential risk assessment, the TCVP powder and pump spray post-application exposure study was not conducted in a manner reflective of current standards that require a defined stroking procedure and greater number of petting simulations. In order to account for this difference, the agency used the maximum observed percent residue transfer on the day of product application (Day 0) for both formulations for exposure and risk quantification. Typically, the agency assesses post-application risk with use of the mean percent residue transfer measured on Day 0;

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[25] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[26] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

[27] W. Britton, Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589.

the use of the maximum value results in a more health protective risk assessment. Even though the post-application exposure study methods have evolved, the TCVP study employed a rigorous collection method and is not anticipated to underestimate exposure.

The 2012 Residential SOPs: Treated Pets recommends assessment of post-application exposures using day of application (i.e., Day 0) residue transfer -- defined as fraction application rate ($F_{AR}$) in the 2012 SOPs. Day of application (Day 0) percent residue transfer values used in the 2014 residential risk assessment for exposure/risk quantification of dusts/powders and pump/triggers sprays are as follows: dusts/powders, 0.048% (maximum observed) and pump sprays, 0.81% (maximum observed).

*Pet Collar Exposure Data Source:* The 2015 draft ORE assessment for Registration Review used both the Davis study and an amitraz pet collar residue transfer study for assessment of non-cancer residential post-application risks following contact with pets treated with TCVP pet collars. The Davis study publication was considered for use in the assessment due to arguments submitted by NRDC in its August 5th, 2015, Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.) (Opening Brief). NRDC's Opening Brief was filed in litigation challenging EPA's Nov. 6, 2014 denial of NRDC's 2009 petition to cancel all TCVP pet products; the denial was based on the 2014 residential pet product assessment. The agency provided a point-by-point response to the NRDC's arguments in a Dec. 21, 2015 memorandum,[28] issued in conjunction with the Dec. 21, 2015 Draft TCVP Risk Assessment for Registration Review. Among the arguments presented by NRDC was that the agency "failed to consider the Davis study for the estimation of post-application risks for exposures to the TCVP pet collar." In its 2015 memorandum, the agency acknowledged consideration of the potential effect of using the Davis study as the basis for residential post-application assessment of exposures from TCVP pet collars, the study was reviewed,[29] an OPP ethics review was conducted[30], and preliminary risk estimates were presented with use of these data. However, the formal use of the Davis study was put on hold pending review by EPA's HSRB in January 2016. The Davis study includes 1) glove residue data collected by adult volunteers petting TCVP treated dogs 2) plasma cholinesterase (ChE) measures from treated dogs 3) tee shirt samples collected from children exposed to TCVP treated dogs and 4) urinary biomonitoring for adults and children exposure to TCVP treated dogs. However, for purposes of the TCVP risk assessment, EPA may rely only on the transferable residue data [in light of 40 CFR Part 26, subpart Q regarding ethical standards for assessing whether to rely on the results in human research in EPA actions] as these are the only data from the study that result in the potential for greater risks, are applicable to human exposures (in the case of the dog plasma ChE measures), or in the case of the urinary biomonitoring data, are useful given current scientific limitations (i.e., a physiologically based pharmacokinetic (PBPK) model applicable to TCVP). While EPA proposed to rely only on the

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[28] W. Britton. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589.

[29] W. Britton. Science Review of "Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos" for HSRB Consideration. D430707. 12/16/2015.

glove residue data (which did not involve children), since these data were collected as part of broader research which did involve children, HSRB review was necessary.

On January 12-13, 2016, the EPA HSRB addressed the scientific and ethical charge questions related to Davis study. Ethics and science reviews were conducted by the agency in support of the HSRB meeting.[30,31] A Federal Register (FR) notice was published on 4/11/2016 (69 FR 21335) and provides the following information: EPA's proposal to rely on the Davis study; the reason for review by HSRB; the background on ethical conduct of research; summary of discussion on ethics-related questions; the standards applicable to ethical conduct and reliance on data; and the availability of HSRB meeting materials.[32]

The HSRB concluded that, "The research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol used in the study can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars."[33] Per EPA's response to NRDC's Opening Brief arguments, "EPA would rely on these data (Davis study) for regulatory decision making if HSRB determines that the study is scientifically valid and it meets appropriate human ethics requirements," since these data result in greater potential risks than those estimated using the amitraz pet collar residue transfer study (which had been relied upon in the previous risk assessments). Accordingly, post-application risks have been assessed with use of the Davis study data only and are presented herein.

The use of the Davis study as the primary data source is consistent with, and supported by, the recommendations from the comments following the 2015 draft ORE assessment for Registration Review including those submitted by NRDC and the Hartz Mountain Corporation. Per NRDC, "the Davis Study has met the appropriate scientific and ethical criteria and should be relied upon for the evaluation of exposures from TCVP containing flea collars," and the Hartz Mountain Corporation describes that, "the glove residue data measured in the Davis et al. (2008) study are valuable because they represent actual measurements of TCVP transfer from dogs wearing commercial collars to the hands of individuals petting them." Further, NRDC states that, "EPA's utilization of transferable residue data from the amitraz study is not supported by the evidence and should not be relied upon to evaluate risk."

A summary of the Davis study and a description of how these data have been used for risk quantitation is detailed in Section 5.2 of the corresponding ORE memo (D436833).

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[30] M. Lydon. Ethics Review of Davis et al Research on Flea Collars with TCVP. 12/15/2015.

[31] W. Britton. Science Review of "Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos" for HSRB Consideration. D430707. 12/16/2015.

[32] https://www.federalregister.gov/documents/2016/04/11/2016-08281/tetrachlorvinphos-tcvp-epa-proposal-to-rely-on-data-from-human-research-on-tcvp-exposure-from-flea

[33] Letter from Liza Dawson, PhD, Chair of the EPA HSRB to Thomas Burke, PhD, MPH, EPA Science Advisor. Subject: January 12-13, 2016 EPA Human Studies Review Board Meeting Report. March 30, 2016.

Residential Non-Cancer Post-application Exposure and Risk Equations

The algorithms used to estimate non-cancer exposure and dose for residential post-application can be found in Appendix B of D436833 and the 2012 Residential SOPs.

Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates

*Pet Collars:* As noted above, the post-application assessments for the TCVP pet collars were performed assuming pet collars could be either liquid or solid (dust) formulations, and assuming a varying liquid/dust exposure potential. All child 1 to <2 years old incidental oral exposures to pets treated with pet collars, regardless of the ratio of liquid/dust assumed, are estimated to be of concern (i.e., MOEs < 1000). When assuming a 1/99 liquid/dust formulation ratio, MOEs range from 0.91 to 7.4. When assuming a 50/50 liquid/dust formulation, MOEs range from 1.8 to 15, and when assuming a 99/1 liquid/dust formulation, MOEs range from 65 to 530. A summary of residential post-application exposures and risks from TCVP pet products is presented in Appendix I.

*Dust/Powder and Pump/Trigger Spray*: Residential post-application steady state non-cancer child 1 to < 2 years old incidental oral (hand-to-mouth) exposures to pets treated with TCVP dust/powders are estimated to be of concern (i.e., MOEs < 1000; MOE range from 98 to 640). However, child 1 to < 2 years old incidental oral exposures to pets treated with TCVP pump/trigger spray products are estimated not to be of concern (i.e., MOEs are > 1,000; MOE range from 1,600 to 15,000).

Residential Cancer Post-Application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential cancer post-application risk assessment. All exposure data and assumptions that underlie the residential post-application cancer risk estimates can be referenced in the 2014 residential assessment. Note: For purpose of quantification of estimated TCVP post-application cancer risks, HED used average percent residue transfer data for all days sampled from chemical-specific exposure data for all pet formulations assessed (i.e., the TCVP powder and pump spray study and the Davis study).

Residential Cancer Post-application Exposure and Risk Estimate Equations

As was done for residential handlers, cancer post-application risk estimates for adults were calculated using a linear low-dose extrapolation approach in which a LADD is first calculated and then compared with a $Q_1$* that has been calculated for TCVP based on dose response data in the appropriate toxicology study ($Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$). The algorithms used to estimate the LADD and cancer risk for residential post-application exposure can be found in Appendix B of D436833.

It should be noted that in the past, cancer risk assessments have assumed that children are no more sensitive than adults to carcinogens (i.e., no adjustment was made to children's exposure estimates in calculating a cumulative lifetime exposure). More recently, the agency's

"Guidelines for Carcinogen Risk Assessment" (USEPA, 2005) and "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens" (USEPA, 2005) proposed age-dependent adjustment factors to be applied to children's exposure. These age-dependent factors are applied only to carcinogens shown to have a mutagenic mode of action. In general, most carcinogenic pesticides have not been shown to act through a mutagenic mode of action, and thus separate assessment of children and adults is not warranted. Any pesticide found to be a carcinogen acting through a mutagenic mode of action should be dealt with on a case by case basis, and such an assessment should follow the agency's 2005 guidance. Once the results of the newly-required mutagenicity studies have been submitted and reviewed, the need for an updated cancer assessment will be determined.

Summary of Residential Post-application Cancer Exposure and Risk Estimates

*Pet Collars:* Residential cancer (adult only) risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio range from $10^{-5}$ to $10^{-4}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1 liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$.

*Dust/Powder and Pump/Trigger Spray:* Residential cancer (adult only) risks estimated for TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$.

Adult residential post-application dermal cancer risk estimates are presented in Appendix J.

## 6.3 Spray Drift

A quantitative spray drift assessment was not conducted because the use of TCVP for direct animal treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs are either 1) not applied via aircraft, groundboom, or airblast equipment or 2) for applications to poultry buildings with groundboom equipment, the use is indoors and not anticipated to be a significant source of spray drift.

## 6.4 Residential Bystander Post-Application Inhalation Exposure

A quantitative residential post-application inhalation exposure assessment was not performed, as inhalation exposure is expected to be negligible from applications to pets.

# 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, for food use pesticides, aggregate risk assessment must consider exposures from three sources: food, drinking water, and residential uses. These exposures could occur from three major routes: oral, dermal, and inhalation. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating



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exposures and risks from various sources, HED considers both the route and duration of exposure.

## 7.1 Acute Aggregate Risk

The acute aggregate risk assessment combines exposures to TCVP from food and drinking water. While drinking water exposures alone were not of concern, there are acute risk estimates of concern for food only; therefore, a quantitative acute aggregate risk assessment was not conducted.

## 7.2 Steady State Aggregate Risk

The steady state aggregate assessment includes the steady state dietary (food and water) and residential exposures. However, because there are risks of concern associated with both dietary (food) and residential exposure, a quantitative steady state aggregate risk assessment was not conducted.

## 7.3 Cancer Aggregate Risk

The cancer aggregate risk assessment combines residential and dietary (food and drinking water) expected lifetime exposures for adults. For TCVP, a cancer aggregate assessment was performed for adult handlers and for adult post-application activities related to residential pet product use.

The residential handler cancer aggregate assessment uses exposures from applying TCVP products to pets (collars, dust/powders, and pump/trigger sprays). Residential handler cancer (dermal) risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio are all $10^{-7}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$. Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$. The cancer dietary (food and drinking water) assessment resulted in an estimated risk of $9 \times 10^{-7}$. The cancer aggregate assessment combines the highest (worst case) handler exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type.

The cancer aggregate (dietary and residential exposures) risk estimates for handlers are in the $10^{-7}$ to $10^{-6}$ range and are presented in Table 7.3.1.

The residential post-application cancer aggregate assessment uses dermal exposures from contacting pets treated with TCVP products (collars, dust/powders, and pump/trigger sprays). Residential cancer post-application risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio range from $10^{-5}$ to $10^{-4}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1



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liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$. Post-application cancer risks estimated for handlers of the TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$. The cancer aggregate assessment combines the highest (worst case) post-application exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type.

The cancer aggregate (dietary and residential exposures) post-application risk estimates are in the $10^{-6}$ to $10^{-4}$ range and are presented in Table 7.3.2.

**Table 7.3.1. Adult Handler Aggregate Cancer Risk Estimates for TCVP Pet Products**
***(Risk is estimated using a Q* of 0.00183)***

| Product Formulation Type | Reg No.; Animal type; Animal size | Food and Water Exposure (mg/kg/day)[1] | Residential Exposure (LADD, mg/kg/day)[2] | Aggregate Cancer Risk (food, water, residential) |
|---|---|---|---|---|
| **Pet Collar** (1/99 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $1.1 \times 10^{-4}$ | $1 \times 10^{-6}$ |
| **Pet Collar** (50/50 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $5.9 \times 10^{-5}$ | $1 \times 10^{-6}$ |
| **Pet Collar** (99/1 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $8.5 \times 10^{-6}$ | $9 \times 10^{-7}$ |
| **Dust/Powder** | 67517-82: Dog; Large | $5.1 \times 10^{-4}$ | $2.3 \times 10^{-4}$ | $1 \times 10^{-6}$ |
| **Pump/Trigger Spray** | 2596-125, -140: Dog (Trigger); Large | $5.1 \times 10^{-4}$ | $3.9 \times 10^{-5}$ | $1 \times 10^{-6}$ |

[1] Table 5.4.5.1
[2] Appendix D of ORE Memo D436833.
[3]Aggregate Cancer Risk = ($Q_1$*) (Food & Water Exposure + Residential LADD)

**Table 7.3.2. Adult Post-Application Aggregate Cancer Risk Estimates for TCVP Pet Products**
***(Risk is estimated using a Q* of 0.00183)***

| Product Formulation Type | Reg No.; Animal type; Animal size | Food and Water Exposure (mg/kg/day)[1] | Residential Exposure (LADD, mg/kg/day)[2] | Aggregate Cancer Risk (food, water, residential) |
|---|---|---|---|---|
| **Pet Collar** (1/99 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $3.4 \times 10^{-1}$ | $6 \times 10^{-4}$ |

| Table 7.3.2. Adult Post-Application Aggregate Cancer Risk Estimates for TCVP Pet Products *(Risk is estimated using a Q* of 0.00183)* | | | | |
|---|---|---|---|---|
| **Product Formulation Type** | **Reg No.; Animal type; Animal size** | **Food and Water Exposure (mg/kg/day)[1]** | **Residential Exposure (LADD, mg/kg/day)[2]** | **Aggregate Cancer Risk (food, water, residential)** |
| **Pet Collar** (50/50 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $1.8 \times 10^{-1}$ | $3 \times 10^{-4}$ |
| **Pet Collar** (99/1 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $1.6 \times 10^{-2}$ | $3 \times 10^{-5}$ |
| **Dust/Powder** | 2596-78: Cat; Small | $5.1 \times 10^{-4}$ | $1.9 \times 10^{-3}$ | $2 \times 10^{-6}$ |
| **Pump/Trigger Spray** | 2596-126, 140: Cat (Trigger); Small | $5.1 \times 10^{-4}$ | $5.3 \times 10^{-4}$ | $2 \times 10^{-6}$ |

[1] Table 5.4.5.1
[2] Appendix F of ORE Memo D436833.
[3]Aggregate Cancer Risk = ($Q_1$*) (Food & Water Exposure + Residential LADD)

## 8.0 Occupational Exposure/Risk Characterization

Occupational and Residential Exposure Memo: D436833, 12/21/2016, W. Britton.

Occupational handler risks have been updated herein to reflect changes in the policy used for inhalation assessment since the 2015 ORE assessment. Previously, HED was using multiple human equivalent doses (HEDs) specific to different handler activities. The current policy recommends that only a single HED is necessary to assess all potential occupational handler activities. All other occupational handler data, assumptions, and algorithms used for the 2015 ORE assessment remain the same.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

### 8.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

***Mixer/Loaders:***

(1a) Liquid: Groundboom Applications
(1b) Liquid: Paint Applications
(2a) Wettable Powder: Groundboom Applications
(2b) Wettable Powder: Paint Applications
(3a) Dust: Paint Applications

***Applicators:***

(4) Groundboom Applications
(5) Open Pour Liquid Additive for Feed Through
(6a) RTU Pet Collar – 1/99 Liquid/Dust Formulation
(6b) RTU Pet Collar – 50/50 Liquid/Dust Formulation
(6c) RTU Pet Collar – 99/1 Liquid/Dust Ratio Formulation
(7) RTU Dust/Powder – Pets
(8) RTU Pump/Trigger Sprays - Pets

***Mixer/Loader/Applicators:***

(9a) Liquid: Backpack Sprayer
(9b) Liquid: Manually-Pressurized Handwand
(9c) Liquid: Mechanically-Pressurized Handgun
(9d) Liquid: Backrubber or Facerubber
(10a) Wettable Powder: Backpack Sprayer
(10b) Wettable Powder: Manually-Pressurized Handwand
(10c) Wettable Powder: Mechanically-Pressurized Handgun
(10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary)
(10e) Wettable Powder: Rotary Duster
(10f) Wettable Powder: Plunger Duster
(11a) Dust: Self-Treating Dust Bag
(11b) Dust: Shaker Can
(11c) Dust: Rotary Duster
(11d) Dust: Plunger Duster
(12a) Paint: Brush or Roller
(12b) Paint: Airless Sprayer
(13) Solid Feed Additive for Feed Through: Cup

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis. Application rate: A summary of all TCVP occupational use sites and application rates is presented in Appendix A of D436833.

*Pet Collar Formulation Assumptions:* As was mentioned in the residential sections, due to the uncertainty associated with whether TCVP pet collars are liquid and/or dust formulated products, handler steady state inhalation exposures for TCVP pet collar application were assessed assuming pet collars could be liquid and solid (dust) formulations concurrently with varying ratios of liquid/dust. The liquid formulation UE data assumes negligible inhalation exposure; therefore, only the dust-specific UE data is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure.

*Unit Exposures:* It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[34]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the agency website[35].

A single chemical-specific exposure study, Monitoring Exposure of Mixer/Loaders and Applicators Treating Agricultural Premises with Tetrachlorvinphos (Rabon® 50 WP Insecticide) in Handheld Wand-Type Sprayers (MRID 42622301), was used as appropriate (i.e., exposure scenario 10c, mix/load and apply WP with mechanically-pressurized handgun) in the most recent occupational risk assessment for TCVP.[36] Per the prior risk assessment, risks for the exposure scenario were estimated with use of the chemical-specific exposure data as well as surrogate PHED data. This exposure study was summarized in the 2015 draft ORE assessment Registration Review[37].

The PHED data recommended for the exposure scenario reflects unit exposure values (dermal and inhalation) that represent an individual conducting all activities, mixing/loading/applying, for use of the WP product by mechanically pressurized handgun. In contrast, the chemical-specific exposure study was conducted in a manner which separated out the mixing/loading and application components of the exposure scenario. Exposure scenario 10c has been assessed, and estimated risks presented separately, (i.e., mixer/loader and applicator) with use of the chemical-specific data, and for all activities with use of PHED. When applied, the dermal and inhalation unit exposures resulting for product application result in risk estimates that are very similar to risk estimates using the PHED data. Non-cancer and cancer private/farmer and

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[34] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[35] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html
[36] J. Dawson. Tetrachlorvinphos: Further Revisions to Occupational Risk Assessment for Uses in the Poultry and Cattle Production Industries. 3/28/2002. D281972.
[37] W. Britton. Tetrachlorvinphos: Occupational and Residential Exposure Assessment for Registration Review. 12/21/2015. D426984.

contract/commercial occupational handler risk estimates for exposure scenario 10c are presented separately from the risk summaries for all other occupational handler exposure scenarios in Appendix K: Table K.2 and Appendix L: Tables L.2 and L.4, respectively.

In some cases, due to the lack of data for an exposure scenario or the unique nature of the scenario, surrogate exposure data were used as follows:

- Exposure data for the loading/application of dust formulations were used as a surrogate for the loading/application of wettable powders for rotary and plunger duster applications (10e, 10f). For exposure scenario 10e, exposure data for plunger dusters were used due to the lack of data for the rotary duster application method.
- For the assessment of pet collars as a dust formulation, data for applying dusts using a shaker can were used as a surrogate.
- Unlike more typical exposure scenarios where a RTU paint is only loaded or applied, for TCVP the paint must be mixed/loaded for the liquid (1b), wettable powder (2b), and dust (3a) formulations. These exposure scenarios were assessed using the exposure data appropriate for mixing/loading for each formulation with the exception of dust where WP formulation was used as a surrogate for dust.
- For TCVP applications to livestock with a dust formulation via shaker can, a RTU product is not available; therefore, exposures from the mixing/loading of the dust formulation must be assessed in addition to potential exposure resulting from application via shaker can. As a result, the exposure data for the loading/application via a RTU shaker can was used for the assessment of all scenarios relating to the use. The use of these data results in a more protective assessment than would be if the mixing/loading of the dust were assessed separately.
- Exposures from the application of feed (salt or mineral) blocks in livestock – typically, 5 – 15 per head of cattle or horses – is assumed to be negligible if gloves are worn when placing the blocks. Furthermore, for these products the greater majority of the active ingredient is contained within the block, thus further reducing the exposure potential.

*Area Treated or Amount Handled:* The following inputs are consistent with those used in the most recently conducted occupational risk assessment for TCVP and, for those inputs relating to the poultry industry, are reflective of research conducted by BEAD at that time.

- Groundboom: 100,000 square feet for applications to poultry buildings
- Backpack and manually pressurized handwand: 20,000 square feet for applications to poultry buildings
- Mechanically pressurized handwand: 100,000 square feet for applications to poultry buildings
- Backpack, handheld/stationary fogger, manually pressurized handwand, mechanically pressurized handwand, rotary spreader: 20,000 birds for direct application to poultry (i.e., approximately 1 square foot/bird)
- Backrubber/facerubber: 50 gallons
- Paint applications: 2 gallons



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The following inputs are based on either the most recently conducted permethrin occupational and residential exposure and risk assessment for similar use patterns[38] or best professional judgment of product usage:

- All handheld equipment: 400 animals treated daily
- Handheld/stationary fogger: 100,000 square feet to poultry buildings
- Plunger, shaker can, spoon: 1,000 birds or 1,000 square feet
- Pet collar, pump/trigger spray, and shaker can applications: 8 animals treated daily
- Self-treating dust bags: 10 filled daily (assuming a 12.5 lb dust bag)

The following inputs are consistent with EPA regulatory definitions for large concentrated animal feeding operations (CAFOs)[39]. The inputs assume that a single individual is responsible for the food preparation for the entire CAFO and applies the TCVP feed-through products to the animal feed.

- Cup, pour on: 1,000 cows, 500 horses, and 6,250 pigs for liquid and solid feed-through applications. The number of cows and horses represents the maximum identified for large CAFO operations. The number of pigs was estimated by averaging the maximum number weighing over 55 lbs (2,500) and less than 55 lbs (10,000) in large CAFO operations.

*Exposure Duration*: Occupational handler exposure is expected to be short- and intermediate-term in duration. Because of the steady state AChE inhibition exhibited by the OPs, steady state exposures (typically 21 days and longer for OPs, but 1 day to reach steady state for tetrachlorvinphos) were assessed and presented for occupational exposures to TCVP products.

*Mitigation/Personal Protective Equipment:* Estimates of non-cancer inhalation exposure were calculated for various levels of PPE (i.e., respiratory protection). Results are presented for no respirator, PF5 respirator, PF10 respirator, or engineering controls (EC).

The PPE required for occupational use of TCVP varies by formulation type. The respiratory protection required for the occupational handling of TCVP can, at times, differ from label to label with consideration of the same formulation and exposure scenario. Occupational handler exposures are expected from use of TCVP on livestock and pets by livestock handlers, veterinarians, veterinary assistants, and groomers. The pet use formulations include collars, dusts/powders, and pump and trigger sprays. All but one of the TCVP pet product labels do not require PPE, as these are intended for residential sale as well as for occupational use. A summary of PPE required for all TCVP products is presented in Appendix A of D436833.

*Days per Year of Exposure:* To assess cancer risk, it is assumed that private/farmers would be exposed 10 days per year and commercial applicators would be exposed 30 days per year. The

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[38] C. Smith. Permethrin: Third Revision of the Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. 4/4/2006. D325428.
[39] http://www.epa.gov/npdes/pubs/sector_table.pdf

term "private/farmer" means that the applicators or one of the workers would apply the pesticides to land owned or operated by the farmer. Commercial applicators mean the applicators are completing multiple applications for multiple clients.

*Years per Lifetime of Exposure:* It is assumed that handlers would be exposed for 35 years out of a 78-year lifespan.

*Lifetime Expectancy:* Life expectancy values are from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males was 75 years and 80 years for females. Based on the available data, the recommended value for use in cancer risk assessments is 78 years.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix B of D436833.

Combining Exposures/Risk Estimates

Although occupational dermal and inhalation exposures are anticipated for TCVP, risks have been estimated for inhalation exposures only due to the lack of dermal hazard. Therefore, no combined occupational exposures/risk estimates have been quantified.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Of the 198 total occupational handler exposure scenarios assessed, the majority (162) are not of concern (i.e., steady state inhalation MOEs are $\geq$ 300) with currently required personal protective equipment (PPE) (i.e., respiratory protection). Of the remaining 36 handler exposure scenarios, 25 are not of concern with consideration of increasing levels of respiratory protection (i.e., 11 occupational handler exposure scenarios result in estimated risks of concern despite the addition of respiratory protection or engineering controls; MOEs at highest level of respiratory protection range from 3.9 to 280). These eleven handler scenarios include dust formulations (mixing/loading/applying TCVP by rotary duster, self-treating dust bag, or shaker can) and wettable powder formulations (mixing/loading/applying TCVP by mechanically-pressurized handgun using MRID 42622301 and mixing/loading/applying using fogging equipment).

A summary of all non-cancer occupational handler exposure scenarios is presented in Appendix K. For risk management purposes, the currently labeled level of respiratory protection and EC has been identified (shaded) for each individual exposure scenario.

Occupational Handler Cancer Exposure and Risk Equations

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which an LADD is first calculated and then compared with a Q1* that has been calculated for TCVP based on dose response data in the appropriate toxicology study (Q1* = $1.83 \times 10^{-3}$ (mg/kg/day)-1). ADD levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the Q1* to obtain cancer risk estimates. The algorithms used to

estimate the LADD and cancer risk for occupational handlers can be found in Appendix B of D436833.

Summary of Occupational Handler Cancer Exposure and Risk Estimates
Occupational cancer risks were estimated for both private/farmer and contract/commercial handlers. Cancer risks, with currently required PPE, range from $10^{-10}$ to $10^{-5}$ for private/farmer handlers and from $10^{-10}$ to $10^{-4}$ for contract/commercial handlers with currently required PPE.

Unlike the occupational handler non-cancer risk estimates which were based only on inhalation exposures, the occupational handler cancer risk estimates are quantified based on both dermal and inhalation exposures. This is because, despite the determination of the lack of dermal hazard for TCVP, dermal exposures from TCVP must be quantified for the purpose of cancer risk assessment. As previously described, the PPE required for the occupational use of TCVP varies by formulation type. For example, for feed through (solid and liquid food additives) and feed blocks, occupational handlers are required to wear baseline clothing (i.e., long sleeved shirt, long pants, shoes and socks) and gloves. For all other end-use labels with livestock and outdoor perimeter uses, required PPE can vary dependent on the application type or equipment and can range from baseline clothing and gloves, to the addition of coveralls, or respiratory protection.

A summary of occupational cancer risks as estimated at all levels of personal protection and with use of engineering controls is presented in Appendix L. Tables L.1 and L.2 present cancer risks for private/farmer handlers and Tables L.3 and L.4 risks for contract/commercial handlers. For risk management purposes, the currently labeled level of respiratory protection and EC has been identified (shaded) for each individual exposure scenario.

### 8.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties.

Occupational post-application exposures are not anticipated for TCVP as the majority of application scenarios are not to foliar surfaces. The use of TCVP outdoors as a perimeter treatment is not expected to result in occupational post-application exposure as reentry activities related to crop production (e.g., scouting, harvesting) are not anticipated for this use pattern.

## 9.0 Public Health and Pesticide Epidemiology Data

Incident Report Memo: D426986, 5/21/15, S. Recore [40]

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[40] S. Recore *et al.*, 5/21/2015, D426986, Tetrachlorvinphos (TCVP): Tier I Review of Human Incidents for Draft Risk Assessment

HED has prepared a Tier I review of human incidents report. For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient TCVP. The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to TCVP exposure.

The Agricultural Health Study (AHS) is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. TCVP is not included in the AHS, and therefore this study does not provide information for this report.

Although there were a moderate number of TCVP incidents reported to Main and Aggregate IDS (n=374) and SENSOR-Pesticides (n=61), most of these incidents were classified as low severity. The effects experienced were generally minimally traumatic and resolving rapidly and usually involve skin, eye or respiratory irritation. Most of the reported incidents were due to handling and applying TCVP products to pets. Based on the low severity of incident cases reported for TCVP in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. The agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

## 10.0 Cumulative Exposure/Risk Characterization

OPs, like TCVP, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PoDs for each OP, including TCVP. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.5, OPP has retained the FQPA Safety Factor for OPs, including TCVP, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes.

The agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to release of the revised risk assessment. During this period, the agency will determine whether or not it is appropriate to apply the draft guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis for the neurodevelopment outcomes.

## 11.0 Appendices

Appendix A. Toxicology Profile
Appendix B. Results for BMD/BMDL modeling for TCVP
Appendix C. Methodologies for HEC Calculations
Appendix D. Physical/Chemical Properties for Tetrachlorvinphos
Appendix E. TCVP and Metabolites
Appendix F. International MRLs and U.S. Tolerances
Appendix G. Summary of Residential Handler Non-Cancer Exposures and Risk Estimates
Appendix H. Summary of Residential Handler Cancer Exposure and Risk Estimates
Appendix I. Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates
Appendix J. Summary of Residential Post-Application Cancer Exposure and Risk Estimates
Appendix K. Summary of Occupational Handler Non-Cancer Exposures and Risk Estimates
Appendix L. Summary of Occupational Handler Cancer Exposures and Risk Estimates



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## Appendix A. Toxicology Profile and Executive Summaries

### A.1. Toxicology Data Requirements

The requirements (40 CFR 158.500) for the food use for TCVP are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

| Study | Technical | |
|---|---|---|
| | Required | Satisfied |
| 870.1100 Acute Oral Toxicity | yes | yes |
| 870.1200 Acute Dermal Toxicity | yes | yes |
| 870.1300 Acute Inhalation Toxicity | yes | yes |
| 870.2400 Primary Eye Irritation | yes | yes |
| 870.2500 Primary Dermal Irritation | yes | yes |
| 870.2600 Dermal Sensitization | yes | yes |
| 870.3100 90-Day Oral Toxicity in Rodents | yes | yes |
| 870.3150 90-Day Oral Toxicity in Non-rodents | yes | yes [a] |
| 870.3200 21/28-Day Dermal | yes | yes |
| 870.3250 90-Day Dermal | no | - |
| 870.3465 90-Day Inhalation | yes | yes [b] |
| 870.3700a Prenatal Developmental Toxicity in Rodents | yes | yes |
| 870.3700b Prenatal Developmental Toxicity in Non-rodents | yes | yes |
| 870.3800 Reproduction | yes | yes |
| 870.4100a Chronic Toxicity in Rodents | yes | yes |
| 870.4100b Chronic Toxicity in Non-rodents | yes | yes |
| 870.4200a Carcinogenicity in Rats | yes | yes |
| 870.4200b Carcinogenicity in Mice | yes | yes |
| 870.4300 Chronic Toxicity/Carcinogenicity in Rats | yes | yes |
| 870.5100 Mutagenicity—Bacterial Reverse Mutation Test | yes | yes |
| 870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test | yes | yes |
| 870.5375 Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.5xxx Mutagenicity—Other Genotoxic Effects | yes | no[c] |
| 870.6100a Acute Delayed Neurotoxicity in Hens | yes | yes |
| 870.6100b 90-Day Neurotoxicity in Hens | yes | yes |
| 870.6200a Acute Neurotoxicity Screening Battery in Rats | yes | yes |
| 870.6200b 90-Day Neurotoxicity Screening Battery in Rats | yes | yes |
| 870.6300 Develop. Neurotoxicity | yes | yes |
| 870.7485 General Metabolism | yes | yes |
| 870.7600 Dermal Penetration | yes | yes |
| 870.7800 Immunotoxicity | yes | yes |
| Special Studies<br>Comparative Cholinesterase in Rats | yes | yes |

[a] there is a chronic study; [b] 4-Week study

[c] A follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and a study that investigates possible genotoxic activity in the target organ (liver) are required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target).



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## A.2 Toxicity Profiles

| Table A.2.1 Acute Toxicity of Tetrachlorvinphos Technical | | | | |
|---|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No.** | **Results** | **Toxicity Category** |
| 870.1100 | Acute Oral – Rat | 41222504 | $LD_{50}$ =<br>1480 mg/kg (M)<br>465-965 mg/kg (F) | III |
| 870.1200 | Acute Dermal – Rabbit | 41222505 | $LD_{50}$ > 2000 mg/kg | III |
| 870.1300 | Acute Inhalation – Rat | 00138933 | LC50 > 3.61mg/L | IV |
| 870.2400 | Acute Eye Irritation - Rabbit | 41222506 | moderate | III |
| 870.2500 | Acute Dermal Irritation - Rabbit | 41222507 | slight | IV |
| 870.2600 | Skin Sensitization - Guinea Pig | 41377902<br>42981001 | sensitizer | N/A |
| 870.6100 | Acute Delayed Neurotoxicity | 41905901 | No clinical signs of neurotoxicity observed (NTE not measured) | N/A |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3100<br>21-Day Oral Toxicity in (Crl:CD®(SD)IGS BR rats) | 45570601<br>(2001)<br>Acceptable/non-guideline (21-day study; gavage)<br>0, 8, 12, 20, or 50 mg/kg/day | **Repeat exposure**:<br>Brain ChEI NOAEL = 12 mg/kg/day<br>Brain ChEI LOAEL = 20 mg/kg/day, based on brain cholinesterase activity inhibition in females (day 21).<br><br>RBC ChEI NOAEL = 8 mg/kg/day<br>RBC ChEI LOAEL = 12 mg/kg/day, based on RBC cholinesterase activity inhibition in males and females<br>***HIARC: RBC data not reliable***<br>**Single dose exposure**:<br>RBC ChEI NOAEL = 20 mg/kg.<br>RBC ChEI LOAEL = 50 mg/kg, based on RBC cholinesterase activity in both sexes.<br>NOTE: *HIARC: RBC data not reliable from this study.*<br><br>Brain ChEI NOAEL =12 mg/kg.<br>Brain ChEI LOAEL = 20 mg/kg, based on brain cholinesterase activity inhibition (ChEI) in males (22%). At 50 mg/kg, males had 54% and females had 23% brain cholinesterase inhibition.<br><br>$BMDL_{10}$ = 6.7 mg/kg/day<br>$BMD_{10}$ = 9.9 mg/kg/day, based on female RBC ChE inhibition<br>$BMDL_{10}$ = 12.2 mg/kg/day<br>$BMD_{10}$ = 14.7 mg/kg/day, based on female brain ChE inhibition |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3150<br>90-Day Oral Toxicity<br>(Sprague Dawley rats) | 43371201 (1990)<br>Acceptable/guide line<br>0, 100, 2000, or 5000 ppm (diet)<br>Males: 0, 6.7, 142, and 375 mg/kg/day;<br>Females: 0, 10.0, 197, and 467 mg/kg/day.<br><br>$BMDL_{10}$ = 8.0 mg/kg/day<br>$BMD_{10}$ = 10.49 mg/kg/day, based on female RBC ChE inhibition | RBC ChEI NOAEL = 6.7 mg/kg/day<br>RBC ChEI LOAEL = 142 mg/kg/day, based on RBC ChEI in both sexes (males 30%*; females 79%**), bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females and mid-dose males, higher adjusted liver weights (both sexes), higher adjusted adrenal weights in females, and thyroid follicular cell hypertrophy in both sexes. At 467 mg/kg/day, in addition to RBC ChEI in both sexes (males 72%*; females 91%**), females had a 24% brain cholinesterase inhibition, although statistical significance was not attained (females 12%, 14%, 24% brain ChEI with increasing dose; males 1% at HDT). Additionally, decreased body weight was observed throughout the study in males (7%- 12%), with the magnitude of the deficit increasing over time.<br><br>$BMDL_{10}$ = 8.0 mg/kg/day<br>$BMD_{10}$ = 10.49 mg/kg/day, based on female RBC ChE inhibition<br>$BMDL_{10}$ = 26.3 mg/kg/day<br>$BMD_{10}$ = 61.6 mg/kg/day, based on male RBC ChE inhibition<br>No dose-response for brain ChE inhibition (BMD not run) |
| 870.3200<br>21/Day Dermal Toxicity (Crl:CD BR Sprague Dawley rat) | 41342001 (1989)<br>Acceptable/guide line<br>0, 10, 100, or 1000 mg/kg/day<br>6 hours/day, 5 days/week for 15 treatments over a 21-day period | NOAEL = 1000 mg/kg/day<br>LOAEL = not determined.<br>RBC and brain cholinesterase inhibition were not observed in either sex at dose levels up to and including the limit dose.<br><br>Significant dermal effects were not observed. There were no treatment-related effects on body weight, food consumption, hematology or clinical chemistry parameters (except plasma ChE activity), gross or microscopic pathology in either sex.<br>Plasma ChE inhibition was observed in females at 1000 mg/kg/day. |
| 870.3465<br>28-Day Inhalation Toxicity (Sprague-Dawley rat) | 48803501 (2012)<br>Acceptable/guide line<br>nose-only aerosol 6 hours/day, 5 days/week for 3 weeks at exposure concentrations of 0, 0.05, 0.5, or 1.0 mg/L; during the final week of exposure (week 4), the animals were exposed for 7 days | NOAEL= 0.05 mg/L/day<br>LOAEL = 0.5 mg/L/day, based on an increase in RBC cholinesterase inhibition in both sexes. *Brain cholinesterase activity was not monitored.*<br><br>Systemic NOAEL not identified.<br>Systemic LOAEL = 0.05 mg/L, based on diffuse adrenal cortical cell vacuolation in both sexes, enlarged adrenals in females, and increased adrenal weights in females. At 0.5 mg/L and 1.0 mg/L, in addition to the adrenal findings, there was a dose-related increase in vacuolation of the ovaries in females, an increase in squamous metaplasia of the larynx in both sexes, and an increase in follicular cell hyperplasia of the thyroids in both sexes.<br><br>**Sex/Age** \| **Compartment** \| **$BMD_{10}$** \| **$BMDL_{10}$**<br>Female \| RBC \| 0.394 \| 0.050<br>Male \| RBC \| 0.122 \| 0.022 |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3700a Prenatal developmental in (Sprague Dawley Crl:COBS®CD ® (SD)BR)<br><br>TXR# 008124, 008616, 018781 | 40152701 (1987)<br>41828001(1991)<br>41967201 (1991)<br>42520101 (1992)<br>Acceptable/guide line<br>0 (aqueous 0.5% methyl cellulose), 75, 150, or 300 mg/kg/day<br>GD 6-15; 10 mL/kg (gavage) | **Maternal** NOAEL = 75 mg/kg/day<br>**Maternal** LOAEL = 150 mg/kg/day, based on a reduction in BWG/FC*<br>At 300 mg/kg/day, there were clinical signs of toxicity (tremors and chromodacryorrhea)<br>**Developmental** NOAEL =300 mg/kg/day<br>**Developmental** LOAEL = not identified.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).*<br><br>*BWG not considered an adverse effect since BW was not affected. NOAL/LOAEL should be revised to 150/300 mkd. |
| 870.3700b Prenatal developmental in (New Zealand white rabbit) | 00127831 (1982)<br>Acceptable/guide line<br>0, 150, 375, or 750 mg/kg/day (1% CMC)<br>GD 6-19; 5 mL/kg (gavage) | **Maternal** NOEL = 375 mg/kg/day<br>**Maternal** LOEL = 750 mg/kg/day, based on mortality, abortions, and red vaginal fluid.<br>**Developmental** NOAEL = 375 mg/kg/day<br>**Developmental** LOAEL = 750 mg/kg/day, based on an increase in early resorptions and corresponding increase in post implantation loss, and a decrease in live fetuses/doe.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).* |
| 870.3800 Reproduction and Fertility Effects (Charles River CD Crl®SD) BR rats) | 42054301 (1991)<br>acceptable/guidel ine<br>0, 100, 500, or 2000 ppm (diet)<br>F0 Males 0, 5.2, 26, 102 mg/kg/day<br>F1 Males 0, 6.7, 34, 130 mg/kg/day<br><br>F0 Females 0, 7.3, 40, or 155 mg/kg/day<br>F1 Females 0, 8.3, 43, or 168 mg/kg/day | **Parental** NOAEL = 500 ppm (males 26/females 40 mg/kg/day)<br>**Parental** LOAEL = 2000 ppm (males 102/females 155 mg/kg/day), based on decreased body weight gain in F1 generation, increased adrenal weights of F0 females, and decreased body weight gains in F0 males.<br>**Offspring** NOAEL = 2000 ppm (males 102/females 155 mg/kg/day)<br>**Offspring** LOAEL was not identified.<br>**Reproductive** NOAEL = 2000 ppm (males 102/females 155 mg/kg/day)<br>**Reproductive** LOAEL was not identified.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).* |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4100a Chronic Toxicity (Sprague-Dawley rat) | 42980901 (1993)<br>43335101 (1994)<br>Acceptable/guideline<br>0, 100, 1000, or 2000 ppm (diet)<br>Males 0, 4.23, 43.2, or 88.5 mg/kg/day<br>Females 0, 5.93, 62.7, or 125.3 mg/kg/day<br>(2-year study) | NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes); reduced body weight; ~~plasma~~ cholinesterase inhibition in females.<br>RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **); brain ChEI in females at 52 and 104 weeks was 17% and 16% (not **).<br>NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on RBC cholinesterase inhibition in females<br><br>BMD not run due to lack of dose-response |
| 870.4100b Chronic toxicity (Beagle dog) | 42679401 (1993)<br>Acceptable/guideline<br>0, 0, 6.25, 500, 1000 mg/kg/day; (capsule)<br>4/sex/group<br>Cholinesterase pre-test, 12, 26, 52 weeks (plasma, RBC)<br>Brain at termination (1 year) | NOAEL = 6.25 mg/kg/day<br>LOAEL = 500 mg/kg/day, based on plasma cholinesterase inhibition (both sexes), decreased red blood cell counts, hemoglobin, hematocrit, MCHC, MCV, alkaline phosphatase, urine specific gravity, and decreased liver and kidney weights.<br>At 1000 mg/kg/day, increased white blood cell counts (females), increased prostate weight, decreased cholesterol (males).<br>RBC and brain cholinesterase inhibition were not observed at any dose level in either sexes. |
| 870.4200a Carcinogenicity (Sprague Dawley rat) | 42980901 (1993)<br>43335101 (1994)<br>acceptable/ guideline<br>0, 100, 1000, or 2000 ppm (diet)<br>Males 0, 4.23, 43.2, or 88.5 mg/kg/day<br>Females 0, 5.93, 62.7, or 125.3 mg/kg/day<br>104 weeks | NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes); reduced body weight; cholinesterase inhibition in females.<br>RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **); brain ChEI in females at 52 and 104 weeks was 17% and 16% (not **).<br>NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on RBC cholinesterase inhibition in females<br>BMD not run due to lack of dose-response<br>Increased incidence of thyroid C-cell adenomas in male rats at HDT and adrenal pheochromocytomas in males |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4200b Carcinogenicity (B6C3F1 mouse) | 00117443 (1978) Acceptable/guideline 0, 17.5, 64, 320, 1600, 8000, 16000 ppm 0, 2.6, 9.6, 48, 240, 1200, or 2400 mg/kg/day | NOAEL = 1600 ppm (240 mg/kg/day)<br>LOAEL = 8000 ppm (1200 mg/kg/day), based on decreased body weight gain<br>Statistically significant increases in combined hepatocellular adenoma/carcinoma (primarily carcinomas) in female B6C3F1 mice at 1600 ppm.<br>Other doses considered excessive; combined adenomas/carcinomas in males, renal adenomas/carcinomas and combined in males at 16000 ppm |
| 870.4300 Combined Chronic Toxicity/Carcinogenicity (Sprague Dawley rat) | 42980901 (1993) 43335101 (1994) acceptable/guideline 0, 100, 1000, or 2000 ppm Males 0, 4.23, 43.2, or 88.5 mg/kg/day Females 0, 5.93, 62.7, or 125.3 mg/kg/day | See above 870.4200a |
| 870.4200a Carcinogenicity (Osborne-Mendel rats) | 00117443 () Acceptable/non-guideline 0, 4250, or 8500 ppm for 80 weeks | Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. . High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid. Study deficiencies (CPRC, 1988); evidence equivocal. |
| Gene Mutation 870.5100 *Salmonella/Escherichia* bacterial reverse mutation assay | 41222508 (1989) Acceptable/ Guideline 66.7, 100, 333, 667, 1000, or 3300 µg/plate in the presence of or 10, 33.3, 66.7, 100, 333, or 667 µg/plate absence of mammalian metabolic activation (S9-mix) | Strains TA98, TA100, TA1535, TA1537, and TA 1538 of *S. typhimurium* were exposed to TCVP from concentrations of 66.7 to 3300 µg/plate in the presence and 10-667 µg/plate absence of mammalian metabolic activation (S9-mix).<br>There was no evidence of induced mutant colonies over background. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| *In vitro* mammalian cytogenetics 870.5375 Chinese hamster ovary cells | 41312901 (1989) Acceptable/ Guideline Concentrations of 22.9, 44.9, 59.9, 79.8, or 99.8 µg/mL without S9; 12.5, 25, 37,6, or 75.1 µg/mL in the presence of S9-mix. | Positive for inducing chromosomal aberrations at 59.9, 79.8 and 99.8 µg/mL in absence of metabolic activation, but negative at 29.9 or 44.9 µg/mL in absence of metabolic activation.<br>Negative for inducing chromosomal aberrations at 12.5, 25, 37.6, or 75.1 µg/mL in the presence of rat S9 metabolic activation. |
| Unscheduled DNA Synthesis 870.5550 in mammalian cells in culture | 42156401 (1992) Acceptable/ Guideline Doses of 5, 7.5, 10, 15, 20, 23, 25, 27, 30, 35, or 40 µg/mL of TCVP. | Concentrations of 35 and 40 µg/mL were lethal. Results were negative. |
| 870.6100 Acute and 28-Day Delayed Neurotoxicity (Domestic hen) | 41905901 (1990) Acceptable/guide line 2500 mg/kg x 2 (21 days apart) | Does not cause delayed neurotoxicity; 4/15 died. |
| 870.6200a Acute Neurotoxicity Screening Battery (Sprague-Dawley Crl:CD®BR rats) | 42912501 (1993) Acceptable/guide line 0, 65, 325, or 650 mg/kg (gavage) | NOAEL = 65 mg/kg<br>LOAEL = 325 mg/kg, based on transient neurotoxic effects in both sexes consistent with cholinesterase inhibition. No neuropathological effects.<br><br>*Cholinesterase activity was not monitored in the study.* |
| 870.6200b Subchronic Neurotoxicity Screening Battery (Crl:CD® BR rats) | 43294101 (1994) Acceptable/guide line 0, 200, 1000, or 5000 ppm (diet) (0, 100, 500, or 250 mg/kg/day; standard conversion) | NOAEL = 5000 ppm (250 mg/kg/day); HDT<br>LOAEL = not identified.<br><br>*Cholinesterase activity was not monitored in the study.* |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.6300 Developmental Neurotoxicity (Crl: CD® (SD)IGS BR VAF/Plus® rats) | 46660601 (2005) acceptable/guideline<br>0, 10, 50, or 200 mg/kg/day<br>GD 6 –LD 6 (gavage)<br>46791401 (2006) +control data | **Maternal** NOAEL = 200 mg/kg/day<br>LOAEL = not identified.<br>**Offspring** NOAEL = 50 mg/kg/day<br>LOAEL = 200 mg/kg/day, based on deceased body weight, body weight gain, several morphometric linear brain measurements in both sexes, and decreased absolute brain weight in males on PND 70<br>*Cholinesterase activity was not monitored in the study.* |
| 870.7485 Metabolism and Pharmacokinetics (Sprague-Dawley CD rat) | MRID 41988401 (1991) Acceptable/guideline<br>5 mg/kg [single and repeat (14 days)] and 250 mg/kg (single) | Most of radioactivity recovered in urine (46%-60%) and feces (38%-56%) within 48 hours post dose; major metabolite in urine was trichloromandelic acid (18%-26%); major metabolite in feces was trichlorophenylethanol (>13%).<br>Since the oral LD50 for female rats is lower than the male LD50, it is noteworthy that males of all groups excreted more total label as trichloromandelic acid, a more completely metabolized form of TCVP; high-dose females tended to excrete more of the label as desmethyl TCVP (with the phosphate group still attached to the remainder of the molecule), a compound that could be derived from TCVP with only a single metabolic step. |
| 870.7600 Dermal Penetration (Sprague Dawley CD rats) | MRID 42111501 (1991)<br>MRID 41862401 (1991) Acceptable/Guideline<br>0, 0.01, 0.1, 1, or 5 mg/cm$^2$ for exposures of 0.5, 1, 2, 4, and 10 hours and 10 hour wash with 72 hour exposure | Absorbed dose following 0.01 mg/cm$^2$ dose is 9.57% following 10-hour exposure. |
| 870.7800 Immunotoxicity (Crl:CD-1(ICR) female mouse) | 48794701 (2012) acceptable/guideline<br>0, 75, 300, 1200 mg/kg/day | Systemic NOAEL = 1200 mg/kg/day,<br>Systemic LOAEL = not identified.<br>Immunotoxicity NOAEL = 1200 mg/kg/day.<br>Immunotoxicity LOAEL = not identified. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special study Comparative cholinesterase<br><br>*gestational CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus rats) | MRID 48291101 (2010) Acceptable/non-guideline<br>1% aqueous (w/v) methylcellulose<br>0, 75, 150, 300 mg/kg/day<br>GD 6-21 (gavage) | The main purpose of this study was to determine whether there is differential sensitivity between dams and fetuses with respect to cholinesterase inhibition following oral exposure to TCVP.<br>***RBC ChE***: Neither the dams nor the fetuses demonstrated RBC ChE inhibition at dose levels where RBC ChE inhibition (ChEI) would be expected. The repeat dosing study (2012, 48773401) conducted in the same laboratory in the same strain of rat clearly demonstrated RBC ChE inhibition at 50 and 200 mg/kg/day in female rats. In the gestational/fetal study, RBC results in the dams were ↓5.1%, ↓15%, and ↓3% RBC ChEI, with increasing dose. The fetal RBC data were of little value because only one or two fetal samples were available for the control, low, and high dose groups and no sample was available for the mid dose group. *There was no way to compare adult and fetal RBC ChE.*activity<br>***Brain ChE.*** Brain ChE inhibition was dose dependent in dams (↓31%, ↓44% and ↓67% with increasing dose). Fetal brain ChE values (↓20%, ↓20.9% and ↓20.8%, with increasing dose) showed no dose-response and are questionable. However, the data suggest that the fetal brain ChE is not more sensitive to inhibition by TCVP than the dams.<br>***Plasma ChE***. Plasma ChE inhibition in dams was dose dependent ↓62%, ↓71% and ↓77%, with increasing dose). Fetal plasma ChE values were ↓22%, ↓18.5% and ↓20.8%, with increasing dose. The lack of a dose response raises questions as to whether these lower values are actually inhibition. However, the data do not indicate that the fetuses are more sensitive than the dams.<br><br>***Classification:*** This *in vivo* comparative ChE study is classified as **Acceptable/non-guideline**. The inability of the laboratory to detect RBC ChE in the dams and the flat dose response curves for the brain ChE in both pups and adults confounds the interpretation of the study. However, no additional gestational CCA study is being requested at this time because there is no indication that the fetuses were more sensitive than the dams. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special studies Comparative cholinesterase<br><br>*Acute CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain rat) | MRID 48294601 (2010) Acceptable/non-guideline<br>Single gavage dose (1% aqueous methylcellulose) young adult, PND 11, PND 21 0, 75, 150 or 300 mg/kg | The main purpose of this study was to determine whether there is differential sensitivity among the PND11, PND21 and adults with respect to cholinesterase inhibition following exposure to TCVP.<br>Overall, there is little confidence in the ChE data mainly because of the lack of clear dose and temporal responses. The number of samples in many cases was inadequate due to sample loss (no sample available, 1, 2, or 3 samples). Also, duplicate samples that did not replicate contributed to the low number of samples available for a meaningful assessment. Brain ChE assessment also appeared to be affected by the low number of samples. The results for all three enzyme sources indicated that there was inhibition at all doses but there was poor dose response with the degree of apparent inhibition at the higher doses often less that at the low dose of 75 mg/kg/day. There was also a lack of temporal concordance with high apparent inhibition at one time, a much lower degree at the following time point, and back to the higher level at the next time point. Further, there was more or similar apparent inhibition at the low dose of 75mg/kg in this acute study than there was in the repeat dosing study (2012, MRID 48773401, eleven daily doses) at 200 mg/kg/day and in the gestational study (2010, MRID 48291101, fifteen daily doses). It is noted that the repeat dosing study indicated that there was no increase in sensitivity of the pups relative to the adults with regard to ChEI by TCVP. However, in this acute study, there were several comparisons among the PND11, PND21 and adults that suggested the pups were more sensitive. Although there is little confidence in the ChEI data in this study, no additional acute CCA study is being requested at this time.<br>***Benchmark Dose (BMD) modeling.*** BMD modeling was performed but could not be done with the RBC data or for the PND11 brain data because of too few samples and/or the data would not otherwise fit the models. BMD modeling for the brain ChE data (3-hour time point) indicated that for males, the adults were slightly more sensitive than the PND 21 pups but the females were considered similar with respect to the $BMD_{10}$ and $BMDL_{10}$.<br><br>**TCVP/Study** \| **Sex/Age** \| **Compartment** \| **BMD Results** (mg/kg/day) \| **$BMD_{10}$** \| **$BMDL_{10}$**<br>MRID 48294601 Acute CCA \| Adult male \| Brain \| 6.76716 \| 5.02249<br>MRID 48294601 Acute CCA \| Adult female \| Brain \| 11.2932 \| 4.55107<br>MRID 48294601 Acute CCA \| Male pup PND 21 \| RBC \| 16.8647 \| 9.71265<br>MRID 48294601 Acute CCA \| Female pup PND 21 \| Brain \| 9.80073 \| 4.6942<br>MRID 48294601 Acute CCA \| Male pup PND 21 \| Brain \| 11.246 \| 6.76389<br><br>This study is classified as **Acceptable/Non-Guideline.** There is too much variability in the ChE data to make meaningful comparisons for sensitivity for RBC and brain ChE inhibition. Although there is little confidence in the ChEI data in this study, no additional acute CCA study is being requested at this time. **UPDATE: another acute CCA study report was identified (MRID 48773401a); see below.** |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special studies Comparative cholinesterase acute CCA<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain | 48773401a (2012) Acceptable/Non-guideline. 0, 5, 10, 50 or 200 mg/kg/day single gavage dose (1% aqueous methylcellulose; 10 mL/kg) young adult, PND 11 pups, PND 21 pups | The NOAEL for adult rats (both sexes) for RBC and brain cholinesterase inhibition following an acute oral dose was not determined. The LOAEL for adult rats is 10 mg/kg.<br><br>The NOAEL for PND 21 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg.<br><br>The NOAEL for PND 11 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg. |

| TCVP/Study | Sex/Age | Compartment | BMD Results (mg/kg) | |
|---|---|---|---|---|
| | | | $BMD_{10}$ | $BMDL_{10}$ |
| MRID 48773401a Acute CCA | Male PND11 | Brain | 5.1 | 4.5 |
| | Female PND11 | Brain | 5.9 | 4.8 |
| MRID 48773401a Acute CCA | Male PND11 | RBC | 5.0 | 4.1 |
| | Female PND11 | RBC | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | Male PND21 | Brain | 3.5 | 3.2 |
| | Female PND21 | Brain | 5.3 | 3.7 |
| MRID 48773401a Acute CCA | Male PND21 | RBC | 3.2 | 2.8 |
| | Female PND21 | RBC | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Male Adult | Brain | 7.4 | 5.6 |
| | Female Adult | Brain | 11.6 | 9.8 |
| MRID 48773401a Acute CCA | Male Adult | RBC | 6.5 | 3.6 |
| | Female Adult | RBC | 14.9 | 11.2 |

| | | |
|---|---|---|
| Special studies Comparative cholinesterase<br><br>*repeat CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain rat) | 48773401 (2012) Acceptable/Non-guideline.<br>0, 5, 10, 50 or 200 mg/kg/day for both ages. | The main purpose of this study was to determine whether there is differential sensitivity between young adults and PND 11 pups with respect to cholinesterase inhibition following repeat oral exposure (11 doses) to TCVP.<br><br>Table 1 shows the adult ChEI data (3 hours after last dose) and Table 2 shows the pup ChEI data. There was a dose-related reduction in RBC and brain cholinesterase activity in both sexes and both age groups |

**Table 1. Inhibition (%) of RBC and Brain ChE Activity in Adult Rats (repeat)**

| Dose (mg/kg/day) | Males | Females |
|---|---|---|
| **RBC** | | |
| 5 | 12% | 8% |
| 10 | 13%* | 8.7% |
| 50 | 30%** | 40%** |
| 200 | 36%** | 62%** |
| **Brain** | | |
| 5 | 2% | - |
| 10 | 7% | 12%* |
| 50 | 14.9%** | 42%** |
| 200 | 17.8%** | 57%** |

**Table 2. Inhibition (%) of RBC and Brain ChE Activity in Pups (repeat)**

| Dose (mg/kg/day) | Males | Females |
|---|---|---|
| **RBC** | | |
| 5 | 2% | - |
| 10 | 2% | - |
| 50 | 33%** | 19%** |
| 200 | 60%** | 62% |
| **Brain** | | |
| 5 | 4% | 4% |
| 10 | 6% | 6% |
| 50 | 16%** | 18.7%** |
| 200 | 46%** | 45%** |

RBC ChE inhibition. At 50 mg/kg/day, both male pups and male adults had similar levels of inhibition (30% to 33%), whereas at 200 mg/kg/day, the male pups were inhibited to ≈60% compared to 36% in the male adult rats. At 50 mg/kg/day, adult females demonstrated more inhibition (≈40%) than the female pups (19%) but at 200 mg/kg/day, both female pups and female adults had ~62% inhibition.
Brain ChE inhibition. Adult females displayed greater brain ChE inhibition at all dose levels than the adult males, whereas a similar magnitude of brain ChE inhibition was observed in male and female pups. Adult females displayed brain ChE inhibition at all dose levels.
A benchmark dose analysis of the cholinesterase data (RBC and brain) was performed that provides both the $BMD_{10}$ and $BMDL_{10}$ of adults and PND11 pups.

**$BMD_{10}$s and $BMDL_{10}$s for Adult Rat and PND 11 Pup Cholinesterase**

| | RBC $BMD_{10}$ | RBC $BMDL_{10}$ | Brain $BMD_{10}$ | Brain $BMDL_{10}$ |
|---|---|---|---|---|
| Adult ♂ | 7.7178 | 3.5942 | 33.803 | 24.4489 |
| Adult ♀ | 8.6762 | 6.1335 | 7.1764 | 5.4980 |
| PND 11 ♂ | 20.4688 | 15.9719 | 33.4825 | 26.5707 |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | | | | | |
|---|---|---|---|---|---|---|
| Guideline No./ Study Type | MRID No. (year)/ Classification /Doses | Results | | | | |
| | | PND 11 ♂ | 20.5608 | 13.1692 | 24.2224 | 18.9412 |
| | | *Overall conclusion.* The main objective of this study was to determine if the pups are more sensitive than the adults to the inhibitory potential of TCVP. Based on assignment of the NOAEL and LOAEL and the BMD modeling, there was no demonstration for increased sensitivity of the pups relative to the adults for either RBC or brain ChE. It is noted, however, that the magnitude of the high dose male pup brain and RBC ChE inhibition is greater than that in the adult males, but the significance is not established. | | | | |

## A.3 Hazard Identification and Endpoint Selection

### A.3.1 Acute Dietary Reference Dose (aRfD) – All Populations

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No**.: 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Data from the young rat from the acute CCA study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations. The study provides the lowest POD following a single dose. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) results in an aPAD of 0.0028 mg/kg/day; the (FQPA) factor may be excluded for the sub-population of adults 50-99 (aPAD of 0.028 mg/kg/day).

### A.3.2 Steady State Reference Dose (ssRfD) –All Populations

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No.:** 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg/day associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Although the steady state dietary endpoint was selected from an acute dose comparative cholinesterase study, the duration of this study is considered appropriate for this exposure scenario since AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose. A longer-term exposure does not result in a lower POD, as evidenced by the larger $BMD_{10}$s found for the repeat dose CCA data.

The point of departure is protective of any exposure duration longer than 21-days, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady state and occurs following one exposure to TCVP. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) results in an ssPAD of 0.0028 mg/kg/day; the (FQPA) factor may be excluded for the sub-population of adults 50-99 (ssPAD of 0.028 mg/kg/day).

### A.3.4 Incidental Oral Exposure (Steady-State)

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No**.: 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Data from the young rat from the acute CCA study are appropriate for the incidental oral assessment since the AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose, and the endpoint is the most sensitive adverse response in all populations. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) is appropriate for incidental oral exposures.

### A.3.6 Dermal Exposure

There is no potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day, and there is no concern for quantitative susceptibility.

### A.3.7 Inhalation Exposure (Steady State)

**Study Selected:** 28-day Inhalation Toxicity Study
**MRID No**.: 48803501
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 0.02 mg/L/day associated with RBC ChE inhibition in both sexes, following inhalation exposure, was selected as a suitable POD for assessing the potential risk associated with inhalation exposure (single day and steady-state). The corresponding $BMD_{10}$ was 0.12 mg/L/day.

**Comments about Study/Endpoint/Uncertainty Factors:** A route-specific, 28-day inhalation toxicity study was used for the steady-state inhalation assessment. Using the Agency's Reference concentration (RfC) methodology, human equivalent concentrations (HECs) and Human

Equivalent Doses (HEDs) was calculated for residential and occupational handlers. Since the inhalation POD is based on a route-specific toxicity study, no absorption factor is necessary to estimate exposure. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

A total uncertainty factor of 30X is appropriate for inhalation exposures [3X for interspecies extrapolation, 10X for intraspecies variation] for adult males and females 49+. The FQPA safety factor (10X) will be retained for infants, children, youths, and women of child-bearing age for all exposure scenarios to account for uncertainties introduced by the lack of sufficient data to quantify potential neurodevelopmental effects observed in epidemiology data on the OP, chlorpyrifos.

## A.4 Executive Summaries

### A.4.1 Subchronic Toxicity

#### 870.3100 90-Day Oral Toxicity – Rat

In a subchronic oral toxicity study (MRID 43371201), tetrachlorvinphos (TCVP; 99% a.i.; Batch KMJ 012) was given to Sprague Dawley rats (10/sex/group) in the diet at doses of 0, 100, 2000, or 5000 ppm (0, 6.7, 142, and 375 mg/kg/day for males; 0, 10.0, 197, and 467 mg/kg/day for females) for 13 weeks.

Survival was not adversely affected in either sex, and there were no clinical signs of toxicity. There were no effects on body weight in the females, but decreased body weight (7%-12%) was observed in males at 5000 ppm throughout the study.

Red blood cell (RBC) cholinesterase (ChE) inhibition was observed in males at 2000 ppm (30%) and 5000 ppm (72%) and in females at 2000 ppm (79%) and 5000 ppm (91%). A noteworthy finding was that 2 rats/sex at 5000 ppm had no measurable RBC ChE activity at 13 weeks. Brain cholinesterase inhibition was observed in females at all dose levels (12%, 14%, 24%, with increasing dose), but statistical significance was not attained at any dose level. Brain cholinesterase inhibition was not observed in males.

Liver weight was increased in females at 2000 ppm (22% when adjusted for body weight) and at 5000 ppm 22%-28%, actual and adjusted). Males displayed an increase in adjusted liver weight (8% and 19% at 2000 ppm and 5000 ppm, respectively). Increased kidney weights were observed in males at 5000 ppm (18% adjusted for body weight), and increased adrenal weights (actual/adjusted) were observed in females at 2000 ppm (20%/28%) and 5000 ppm (28%/32%). There was a dose-related increase in the incidence and severity of bilateral basophilic tubules of the kidneys in males and in the incidence of cellular alteration (fat deposition) in the adrenal cortex of females at 2000 ppm (7/10) and 5000 ppm (9/10). All females at 2000 ppm and 5000 ppm displayed centrilobular hepatocellular hypertrophy, with the severity increasing with dose. In males, the incidence of hepatocellular hypertrophy was significantly increased at 2000 ppm (8/10),

with 2 displaying general cell enlargement, whereas only 1/10 males at 5000 ppm displayed hepatocellular hypertrophy and 7/10 displayed general cell enlargement in the liver. There was a dose-related increase in the incidence of thyroid follicular cell hypertrophy in both sexes.

The NOAEL is 6.7 mg/kg/day, based on RBC ChEI in both sexes (males 30%*; females 79%**), bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females, higher adjusted liver weights (both sexes), higher adjusted adrenal weights in females, and thyroid follicular cell hypertrophy in both sexes at the LOAEL of 142 mg/kg/day. At 467 mg/kg/day, decreased body weight was observed throughout the study in males (7%- 12%), with the magnitude of the deficit increasing over time, females had a 24% brain cholinesterase activity inhibition, although statistical significance was not attained (females 12%, 14%, 24% brain ChEI with increasing dose; males 1% at HDT), and both sexes displayed RBC ChEI (males 72%; females 91%).

This study is classified as Acceptable/Guideline, and it satisfies the guideline requirement (OCSPP 870.3100; OECD 408) for a subchronic oral toxicity study in the rat.

**Single Day and 21-Day Oral Toxicity – Rat**

In a 21-day oral toxicity study (MRID 45570601), tetrachlorvinphos (99.1% a.i., lot #801066) was administered to 18 Crl:CD®(SD)IGS BR rats/sex/dose by gavage at dose levels of 0, 8, 12, 20, or 50 mg/kg/day. Seven or eight animals/sex/group were ***sacrificed approximately 3.5 hours following the first dose*** (time to peak effect); the remaining 10/sex/group were killed after an additional 21 days of dosing. Blood samples were taken for plasma and RBC cholinesterase (ChE) determinations approximately one week prior to study initiation, 3.5 hours following dosing on the first day (day 0), on study days 1, 7, and 14, and at study termination (day 21). Whole brain ChE levels were measured after sacrifice on days 0 and 21.

No treatment-related clinical signs of toxicity or deaths were observed in any animal during daily observations or 1 hour post-dosing. Body weights were similar between the treated and control groups throughout the study.

Dose-related inhibition of ChE activity was observed following both acute and repeated exposures. Inhibition in females occurred at a lower dose than in males. Following a single dose of 50 mg/kg, inhibition of plasma ChE activities (63-67%) relative to concurrent controls were observed in males and females. Also significant inhibition (37-46%) of plasma ChE activities were observed in males and females at 20 mg/kg and in females at 12 mg/kg. However, the LOAEL for plasma ChE inhibition was 8 mg/kg based on inhibition of plasma ChE activity relative to pretest values in males. The NOAEL for plasma ChE inhibition was not established. Significant inhibition (37-46%) of RBC ChE activities from both sexes were observed at 50 mg/kg only. Significant inhibition of whole brain ChE was observed n males at 50 mg/kg (54%) and 20 mg/kg (22%) and in females at 50 mg/kg (23%).

Following repeated exposure, plasma ChE activity in the 20- and 50-mg/kg/day males was similar to the concurrent control levels at each time point with the exception of the high-dose males on day 1 (25% inhibition). However in females, plasma ChE activity was significantly inhibited by 26-30% in the 8-mg/kg/day group beginning on day 14 and by 23-67% in the 12-, 20- and 50-mg/kg/day groups beginning on day 1. Inhibition of RBC ChE levels in 50-mg/kg/day males and females was transient with a maximum inhibition at day 7 (44% and 57%, respectively) followed by modest recovery in males and slight recovery in females. Whole brain ChE activity in males was not affected by repeated exposure. In contrast, significant inhibition of brain ChE activities were observed in the 50 mg/kg/day (36%) and 20 mg/kg/day (16%) females.

**Following both a single and 21-day repeated dose of tetrachlorvinphos, the LOAEL for brain ChE inhibition was 20 mg/kg, based on inhibition of brain ChE activity in males with a NOAEL of 12 mg/kg.**

**Following a single dose of tetrachlorvinphos, the LOAEL for erythrocyte ChE inhibition was 50 mg/kg, based on inhibition of erythrocyte ChE activity with a NOAEL of 20 mg/kg.** Because reproducibility of ChE activity of the rat RBC samples was poor and the standard deviations were large for all groups, the RBC ChE inhibition measurements in the 21-day toxicity study were judged to be unreliable. Therefore, the HIARC (TXR# 0050548; dated March 7, 2002) concluded not to use RBC ChE data from this 21-day study due to lack of confidence in the results.

**Following single and repeated exposure to tetrachlorvinphos, the LOAEL for plasma ChE inhibition was 8 mg/kg, based on inhibition of plasma ChE activity relative to pretest values in males. The NOAEL for plasma ChE inhibition was not established.**

This study is classified as Acceptable/non-Guideline, and it does not satisfy any guideline requirement.

**870.3150 90-Day Oral Toxicity - Dog**

No subchronic study.

**870.3200 21/28-Day Dermal Toxicity - Rat**

In a repeat dose dermal toxicity study (MRID 41342001), male and female Crl:CD BR rats (5/sex/dose) received dermal applications of 0, 10, 100, or 1000 mg/kg/day Rabon Technical (TCVP; 99% a.i.; ) moistened with deionized water for 6 hours/day, 5 days/week for a total of 15 treatments over a 21-day period.

Rabon Technical did not induce significant dermal effects at dose levels up to and including 1000 mg/kg/day. Treatment caused a statistically significant decrease in plasma cholinesterase activity in females at 1000 mg/kg/day. Plasma cholinesterase was also lower than control values for males at the mid and high doses and females at the mid dose; these differences were not statistically significant. TCVP did not result in brain or RBC AChE inhibition, and there were no adverse effects on mortality, body weight, food consumption, hematology, clinical chemistry, organ

weights, or gross and histopathology. The NOAEL is established at 1000 mg/kg/day (the limit dose), since plasma cholinesterase inhibition is not considered a relevant adverse endpoint.

This study is classified as Acceptable/non-Guideline. The study does not satisfy the guideline requirement (OCSPP 870.3200) for a repeat dose dermal toxicity study since an inadequate number of animals per dose were tested; however, the study is adequate for the determination that a dermal risk assessment is not required for TCVP.

### 870.3465 Subchronic Inhalation – Rat

In a nose-only inhalation toxicity study (MRID 48803501), tetrachlorvinphos (TCVP; Lot No. TX 100113; 100% purity) aerosol was administered to male and female Sprague-Dawley rats (10/sex/concentration) for 6 hours/day, 5 days/week for 3 weeks at exposure concentrations of 0, 0.05, 0.5, or 1.0 mg/L. During the final week of exposure (week 4), the animals were exposed for 7 days. An additional 10 rats/sex/concentration were included in the control and high dose groups and sacrificed 14 days after completion of the 28-day exposure period to determine the reversibility of any effects observed. Actual exposure concentrations as measured by HPLC were 100%, 100%, and101% of target values. The mass median aerodynamic diameters (MMADs) ± geometric standard deviations (GSD) were 2.57 µm ±3.785, 4.51 µm ±3.541, and 4.27 µm ±3.343 for the low-, mid- and high concentrations, respectively.

There were no treatment-related deaths. Treatment-related reduced body weights (↓7%* and ↓8%**) and body weight gains (↓27%** and ↓34%***) were observed in males from the mid- and high exposure groups, respectively. The body weight difference persisted through the recovery period in the high-exposure (↓12%) male recovery group, but the weight gain during those 2 weeks was slightly higher (5%) relative to the control group. Bodyweight was comparable among the female groups throughout the study. Body weight gain was reduced in mid- (↓23%) and high (↓32%) exposure females, but body weight gain was comparable to the control during the recovery period. Food consumption was decreased throughout the study in the mid- and high male groups and during the first two weeks in the low dose male group, whereas food consumption was comparable among the female groups. There were no treatment-related findings during the ophthalmoscopic examinations. Decreased hemoglobin concentration and increased platelets were noted in high exposure concentration females, but these findings were no longer evident at the end of the 2-week recovery period. Calcium was slightly, but significantly, elevated in males at all three exposure levels, but there was no dose-response. Cholesterol was significantly elevated in females from the mid- (↑22%) and high (↑27%) exposure groups. These findings were not observed in the recovery group.

Statistically significant RBC ChE activity inhibition ($p<0.001$) was observed in females at the mid- and high exposure concentrations (35% and 30%, respectively). Statistically significant AChE and RBC ChE activity inhibition ($p<0.001$) was observed in males at the mid- and high exposure concentrations (38% and 31% for AChE, respectively; 24% and 31% for RBC ChE, respectively). Plasma acetylcholinesterase activity (58% to 70%) and plasma butyrylcholinesterase activity (66% to 87%) were decreased relative to controls at all exposure

concentrations in females. All cholinesterase activities were lower relative to controls in the male and female recovery groups, but the differences were not statistically significant.

Treatment-related gross findings were limited to discoloration and enlargement of the adrenal glands at the mid- and high exposure concentrations in males, and in females at all exposure concentrations. Diffuse adrenal cortical cell vacuolation (minimal to moderate with an exposure-related incidence) was observed in both males and females at all exposure concentrations. Minimal follicular cell hypertrophy of the thyroid gland was observed with an exposure-related incidence in both sexes at the mid- and high exposure concentrations. Minimal to mild ovarian interstitial cell vacuolation was observed with an exposure-related incidence in females at the mid- and high exposure concentrations. The findings in the thyroid and ovary were referred to as "commonly observed in this strain and age of rat," but no historical control data or literature citations were provided. In the recovery group, 2/5 males and 2/5 females at the high dose had minimal diffuse adrenal cortical cell vacuolation (0/5 incidence in recovery controls). No other treatment-related microscopic findings were observed in the recovery group.

**Based on the effects seen in this study, a systemic NOAEL in male and female Sprague-Dawley rats was not identified. The systemic LOAEL in male and female rats was 0.05 mg/L, based on diffuse adrenal cortical cell vacuolation in both sexes, enlarged adrenals in females, and increased adrenal weights in females. At 0.5 mg/L and 1.0 mg/L, in addition to the adrenal findings, there was a dose-related increase in vacuolation of the ovaries in females, an increase in squamous metaplasia of the larynx in both sexes, and an increase in follicular cell hyperplasia of the thyroids in both sexes.**

**The NOAEL for cholinesterase inhibition was 0.05 mg/L, based on an increase in RBC cholinesterase inhibition in both sexes at 0.5 mg/L/day. Brain cholinesterase activity was not monitored.**

The RBC cholinesterase data from this study have been evaluated using benchmark dose modeling techniques. The results are shown below.

| **$BMD_{10}$/$BMDL_{10}$ Results (mg/L)** | | | |
|---|---|---|---|
| **Sex/Age** | **Compartment** | **$BMD_{10}$** | **$BMDL_{10}$** |
| Female | RBC | 0.394 | 0.050 |
| Male | RBC | 0.122 | 0.022 |

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for a repeat dose inhalation toxicity study.

COMMENT: Although a no effect dose was not identified for the findings in the adrenal (LOAEL 8.7 mg/kg/day), when compared on a mg/kg/day basis to the $BMDL_{10}$ (95% lower confidence limit on the $BMD_{10}$) established for cholinesterase inhibition, the point of departure



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(POD; 1.31 mg/kg/day) used in the inhalation exposure risk assessment is protective of these adrenal findings.

### A.4.2 Prenatal Developmental Toxicity

#### 870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 40152701), tetrachlorvinphos (98.6% ai; Lot No. 10-56-0-0) was administered *via* gavage to groups of 25 Sprague-Dawley Crl:COBS®CD®(SD)BR pregnant rats/groups at dose levels of 0 (0.5% methyl cellulose), 75, 150, or 300 mg/kg/day from gestation day (GD) 6 through GD 15.

All dams survived until study termination. At 300 mg/kg/day, one dam displayed tremors from day 10 onward, and chromodacryorrhea was observed only at this dose level. Although body weights were comparable among the groups, body weight gains were significantly reduced at 300 mg/kg/day throughout the dosing period (52%), and food consumption was also reduced. The numbers of corpora lutea, implantations, resorptions, and dams with liable fetuses were comparable among the groups. The mean number of live fetuses, sex ratio, and fetal body weights were comparable among the groups.

The maternal NOAEL is 150 mg/kg/day, and the maternal LOEL is 300 mg/kg/day, based on tremors and an increased incidence of chromodacryorrhea.

The developmental NOAEL is 300 mg/kg/day, the highest dose tested. A developmental LOAEL was not determined.

The developmental toxicity study in the rat is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; 83-3a) in the rodent when combined with MRID 41828001, MRID 41967201, and MRID 42520101. NOTE: The maternal NOAEL/LOAEL differ from the original assessment due to the current policy that decreases in body weight gain without significant reduction in body weight is not considered an adverse effect.

#### 870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a prenatal developmental toxicity study (MRID 00127831), New Zealand White rabbits (#/sex/dose) were administered tetrachlorvinphos (98% a.i.; T-142-3) by gavage at doses of 0, 150, 375, or 750 mg/kg/day in 5 mL/kg carboxy methylcellulose on gestation days 6-19.

Maternal toxicity at the highest dose tested was manifested as mortality (0/18, 1/18, 1/8, 2/18), abortions (0, 1, 0, 3), and red vaginal fluid (0, 1, 1, 8) in the control, low, mid, and high-dose groups, respectively.

**The maternal NOEL is 375 mg/kg/day, and the maternal LOEL is 750 mg/kg/day.**

Developmental toxicity at the highest dose tested was manifested as an increase in early resorptions/dam (0.4, 0.5, 0.3, 1.4), with a corresponding increase in postimplantation loss (10.6%, 5.6%, 10.5%, 21.9%) and a decrease in live fetuses/dam (7.7, 7.8, 6.9, 5.8) for the control, low, mid, and high-dose groups, respectively.

**The developmental NOEL is 375 mg/kg/day, and the developmental LOEL is 750 mg/kg/day.**

This developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; 83-3b) in rabbits.

### A.4.3 Reproductive Toxicity

#### 870.3800 Reproduction and Fertility Effects - Rat

In a 2-generation reproduction study (MRID 00127831), 28 Charles River CD Crl: (SD) BR Sprague Dawley rats/sex/dose were administered tetrachlorvinphos (99% a.i.; technical Rabon) *via* the diet at doses of 0, 100, 500, or 2000 ppm (F0 males: 0, 5.2, 26, or 102 mg/kg/day/F0 females: 0, 7.3, 40, or 155 mg/kg/day; F1 males: 0, 6.7, 34, or 130 mg/kg/day/F1 females: 0, 8.3, 43, or 168 mg/kg/day). Treatment of the F0 rats began when they were approximately 6 weeks old, and after 10 weeks, they were bred to produce F1 animals. Treatment continued throughout the mating, gestation, and lactation periods, with termination of the F0 rats after weaning of their litters. The F1 rats were weaned onto the same diets as their parents, and groups of 24 rats/sex/dose were selected as the F1 generation. The F1 rats were treated for 11 weeks and then mated to produce F2 litters. Treatment also continued throughout the mating, gestation, and lactation periods. Termination of the F1 and F2 animals occurred at the time of weaning of the litters.

There was no adverse effect on survival, and no clinical signs of toxicity were observed in either generation. Body weights of the adult animals were not adversely affected in either generation. Increased adrenal weights in the F0 females at 2000 ppm were considered treatment-related, although a similar increase in adrenal weight was not observed in the F1 females or in males of either generation. Fertility indices, duration of gestation, mean number of implantation sites, number of stillborns, mean litter size, pup survival, and pup body weights were comparable among the groups in both generations.

**The parental NOAEL is 500 ppm (males 26/females 40 mg/kg/day). The parental LOAEL is 2000 ppm (males 102/females 155 mg/kg/day), based on increased adrenal weights of F0 females**.

**The offspring NOAEL is 2000 ppm (males 102/females 155 mg/kg/day). The offspring LOAEL was not identified.**

**The reproductive NOAEL is 2000 ppm (males 102/females 155 mg/kg/day). The reproductive LOAEL was not identified.**

Note: Although minimal toxicity was observed, and higher doses would have been tolerated, cholinesterase measurements were not performed in this study. Based on findings in other studies in the TCVP database, cholinesterase inhibition would have been observed in this study, if monitored, at the mid and high dose levels.

The 2-generation reproduction toxicity study in the rat is classified Acceptable/Guideline, and it satisfies the guideline requirement for a reproduction toxicity study (OCSPP 870.3800; OECD 416) in the rodent.

### A.4.4 Chronic Toxicity

#### 870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic toxicity/carcinogenicity study (MRID 42980901/43335101), groups of Sprague-Dawley rats (50/sex/group) were administered tetrachlorvinphos (99% a.i.) *via* the diet at dose levels of 0, 100, 1000, or 2000 ppm (males 0, 4.23, 43.2, or 88.5 mg TCVP/kg/day; females 0, 5.93, 62.7, or 125.3 mg TCVP/kg/day) for two years.

Survival was comparable among the groups in both sex, and there were no treatment-related clinical signs of toxicity. Body weight was comparable among the male groups, and females at the high dose displayed slightly lower body weights (8%-12%) than the controls from week 10 on (12% at 52 weeks; 8% at 104 weeks). Food consumption was comparable among the groups.

Females at 2000 ppm had significantly elevated cholesterol levels at weeks 77/78 and 104. Effects at 1000 and 2000 ppm in both sexes included an increased incidence and tendency to greater severity of diffuse lipidosis of the adrenal zona fasciculata, hypertrophy of periacinar hepatocytes, centriacinar degenerative (males only) changes of the liver, and reduced alkaline phosphatase activity.

RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **). Brain cholinesterase inhibition was observed in females at 52 and 104 weeks was 17% and 16% (not **). BMDs were not run due to lack of dose-response in both compartments.

The systemic toxicity NOAEL is 100 ppm (4.23/5.93 mg/kg/day). The systemic toxicity LOAEL is 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes).

Increased incidence of thyroid C-cell adenomas was observed in male rats at the highest dose and adrenal pheochromocytomas were observed in males.(both sexes). The LEL is 1000 ppm, based on decreased body weight in females, histological liver and adrenal changes in both sexes.



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The study is classified Acceptable/Guideline, and it satisfies the guideline requirements for a combined chronic toxicity/carcinogenicity study (OCSPP 870.4300; OECD 453), a chronic oral toxicity study (870.4100; OECD 452), and a carcinogenicity study (870.4200; OECD 451) in the rodent.

#### 870.4100b Chronic Toxicity – Dog

In a chronic oral toxicity study (MRID 42679401), tetrachlorvinphos (TCVP; 99% a.i.; Batch 01-KMJ-012) was given to outbred Beagle dogs (4/sex/group) *via* capsule at doses of 0, 6.25, 500, or 1000 mg/kg/day for 52 weeks.

Survival was not adversely affected in either sex, and there were no clinical signs of toxicity. There were no treatment-related effects on body weight or food or water consumption, and no differences in ophthalmologic, macroscopic, and microscopic findings in either sex.

Treatment-related decreases in red blood cell counts at 500 and 1000 mg/kg/day were corroborated by decreases in hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit, and increases in mean corpuscular volume. The kidney and liver weight increases at 500 and 1000 mg/kg/day in both sexes may be related to the alkaline phosphatase increases (both sexes) and cholesterol decreases (males) observed, but no histopathological correlates were evident. The decreases in urine specific gravity at 500 and 1000 mg/kg/day in both sexes may be related to the kidney weight increases at these dose levels, but histopathological correlates were not evident.

RBC and brain cholinesterase inhibition were not observed at any dose level in either sex at any time point monitored.

The systemic toxicity NOAEL is 6.25 mg/kg/day. The systemic toxicity LOAEL is 500 mg/kg/day, based on decreased red blood cell counts, hemoglobin, hematocrit, MCHC, MCV, alkaline phosphatase, urine specific gravity, and decreased liver and kidney weights.

The chronic toxicity study is classified Acceptable/Guideline, and it satisfies the guideline requirement for a chronic toxicity study (OCSPP 870.4100; OECD 452) in the non-rodent.

### A.4.5 Carcinogenicity

#### 870.4200a Carcinogenicity Study – Rat

In the combined chronic toxicity study (MRID 42980901/43335101), groups of 50 male and 50 female Charles River Sprague-Dawley rats received TCVP in their diet over a 2-year period at 0, 100, 1000 or 2000 ppm (equivalent to 0, 4, 43 and 89 mg/kg/day in males and 0, 6, 63 and 125 mg/kg/day in females, respectively). See above under 870.4100a.

There were increases in the incidences of thyroid C-cell adenomas and adrenal pheochromocytomas in male rats only. Neither of these increases were statistically significant by pairwise comparison to controls, but there was a statistically significant increasing trend for the adrenal tumors.

This study is classified as Acceptable/Guideline, and it satisfies the guideline requirements (870.4200; OECD 451] for a carcinogenicity study in the rat.

In another rat study (MRID 00117443; 1978 NCI-sponsored Gulf South study), Osborne-Mendel rats received TCVP in their diet at doses of 0, 4250, or 8500 ppm for 80 weeks, followed by 31 weeks observation.

Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid.

This study is classified Acceptable/Non-Guideline, and it does not satisfy the guideline requirement (870.4200; OECD 451) for a carcinogenicity study.

### 870.4200b Carcinogenicity – Mouse

In a carcinogenicity study (MRID 00126039), B6C3F1 mice were fed diets containing 0, 17.5, 64, 320, 1600, 8000, or 16000 ppm tetrachlorvinphos for two years in a carcinogenicity study. For systemic toxicity, the NOAEL was 1600 ppm (240 mg/kg/day) and the LOAEL was 8000 ppm (1200 mg/kg/day), based on decreased weight gain. Administration of TCVP in the diet to B6C3F1 mice resulted in statistically significant increases in hepatocellular adenomas, carcinomas and combined adenomas/carcinomas (with carcinomas predominant) in females, and in combined hepatocellular adenomas/carcinomas in males. In male mice there were also statistically significant increases in renal adenomas, carcinomas and combined adenomas/ carcinomas. The statistically significant increases in tumors noted above, all occurred only at doses of TCVP of 8000 ppm or greater, except for the combined hepatocellular adenomas/ carcinomas in female mice, which also occurred at 1600 ppm.

This study is classified as Acceptable/guideline, and it satisfies the guideline requirements (870.4200; OECD 451] for a carcinogenicity study in the mouse.

In another carcinogenicity study (MRID 00117443), B6C3F1 mice were fed diets containing 0, 8000, or 16000 ppm TCVP for 80 weeks, followed by 12 weeks observation. Increased incidences of hepatocellular carcinomas and granulomatous lesions of the liver were found in the dosed mice.

This study is classified Acceptable/Non-Guideline, and it does not satisfy the guideline requirement (870.4200; OECD 451) for a carcinogenicity study in the mouse.

## A.4.6 Mutagenicity

| Summary of the Genotoxicity Studies for TCVP | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| **GENE MUTATION** | | | |
| 870.5100 | Bacterial Reverse Gene Mutation Assay in *Salmonella typhimurium* | 4122508 (1989)<br><br>Acceptable/guideline<br><br>0, 10-667 µg/plate -S9<br>0, 66.7-3300 µg/plate +S9 | **Negative** up to cytotoxic concentrations at the highest dose tested +/-S9 |
| **CHROMOSOME ABERRATIONS** | | | |
| 870.5375 | *In vitro* Mammalian Cell Clastogenicity Assay in Chinese hamster ovary (CHO) cells | 41312901 (1989)<br><br>Acceptable/guideline<br><br>0, 29.9, 44.9, 59.9, 79.8, 99.8 µg/mL -S9 (20-hr cell harvest)<br>0, 12.5, 25, 37.6, 75.1 µg/mL, +S9 (10-hr cell harvest) | **Positive** Significant & dose-related increases in chromosome aberrations in the absence of S9 only after a prolonged exposure due to severe mitotic delay, unhealthy monolayers and reduced mitotic cells at 59.9 & 79.8 µg/mL. Major aberrations: chromatid & chromosome breaks<br>NOTE: Increases in chromosome aberrations were accompanied by marked increases in chromatid & chromosome gaps.<br><br>**Negative** with S9 activation up to a precipitating (≥676 µg/mL) & cytotoxic (2030 µg/mL) concentrations |
| | *In vitro* Mammalian Cell Clastogenicity Assay in Mouse spleen cells | Amer & Aly (1992)<br><br>Acceptable/nonguideline<br>0.25, 0.5, 1.0, 2.0 µg/mL (4-hr treatment) | **Chromosome aberrations**<br>**Positive:** Significant & dose-related increases in chromosome aberrations (minus gaps) at ≥0.5 µg/mL Major aberrations: chromatid & chromosome fragments<br>NOTE: Increases in chromosome aberrations were accompanied by marked increases in chromatid & chromosome gaps.<br><br>**Sister Chromatid Exchange (SCE)**<br>**Positive:** Significant & dose-related increases in SCE induction at ≥0.5 µg/mL |

| Summary of the Genotoxicity Studies for TCVP | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Micronucleus Assay in Bone Marrow Cells of the Mouse | Amer & Aly (1992)<br><br>**Oral:** 0, 3000 & 6000 ppm dietary administration daily for 14 consecutive days or 10 weeks<br>**Ip injection**: 0, 50 & 100 mg/kg weekly for 2 weeks<br>**Dermal:** 0, 1350 mg/kg 4 treatments | **ORAL:** S↑ % PCEs at 3000 & 6000 ppm after 10 weeks at 24 hours & 7 & 14 days post-treatment but **S↑% MPCEs only 6000-ppm group at 24 hours & 7 days post-treatment**<br><br>**IP INJECTION**:<br><br>**<u>50 mg/kg</u>: S↑ % MPCEs at 24 hr. post-treatment (Double injection only); % PCEs not reported.**<br><br>**<u>100 mg/kg</u> (single injection): S↑ % PCEs at 24 hr. post-treatment only.**<br><br>**<u>100 mg/kg</u> (double injection): S↑ % PCEs at 24 hr. post-treatment**<br>**S↑ % MPCEs at 24 hr. post-treatment only.**<br><br>**DERMAL:** S↑ % PCEs at 24 hr. post-treatment 1350 mg/kg (4 applications) only; no increase in MPCEs |
| **OTHER MUTAGENIC MECHANISMS** | | | |
| 870.5550 | *In vitro* unscheduled DNA synthesis (UDS) in primary rat hepatocytes | 42156401 (1992)<br><br>Acceptable/guideline<br><br>0, 10-40 µg/mL (9 doses) | **Negative**<br>Cytotoxicity was observed as follows: 35 & 40 µg/mL -lethal<br>23-30 µg/mL (moderate to high cytotoxicity)<br>15 & 20 µg/mL (slight cytotoxicity)<br>10 µg/mL (non-cytotoxic) |
| | DNA adduct formation<br>Swiss male mice<br>liver. | Zayed et al., 1983)<br>25, 50 and 100 mg/kg i.p. injection | **Positive**<br>Fraction of total applied dose associated with 7-methyl guanine was estimated to be $9x10^{-5}$ and $39x10^{-5}$ in DNA and RNA, respectively |

The relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[41].

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[41] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

## A.4.7 Neurotoxicity

### 870.6100b Delayed Neurotoxicity – Hen

In an acute delayed neurotoxicity study in hens (MRID 41905901), technical Rabon (tetrachlorvinphos; Lot # 01-KMJ-012; 99% a.i.), was administered twice orally (Mazola corn oil) to hens at 2500 mg/kg, with an intervening 21-day period (total dose 5000 mg/kg).

There was sufficient evidence of acute toxicity, including mortality (4/15), to establish that the test material was administered at a sufficiently high dose. TCVP did not result in delayed neurotoxicity, as evidenced both by in-life observations and microscopic examination of spinal cord tissue from three levels. The minimum myelin degeneration seen in 2 hens was consistent with the normal background incidence for this finding in this type of study. The positive control material (tri-0-tolyl- phosphate, TOTP) at 1000 mg/kg elicited the appropriate response.

This study is classified **as Acceptable/Guideline** and it satisfies the guideline requirement for a delayed neurotoxicity study in the hen (870.6100).

### 870.6200a Acute Neurotoxicity Screening Battery – Rat

In an acute neurotoxicity study (MRID 42912501), tetrachlorvinphos (99% a.i.; Lot #: 01-KMJ-012) was administered *via* gavage (10 mL/kg; in corn oil) to non-fasted Sprague-Dawley Crl:CD®BR rats (12/sex/dose) at doses of 0, 65, 325, or 650 mg/kg. All rats were evaluated in functional observational batteries and motor function observations on days 0, 7, and 14.

Transient neurotoxic effects were observed in both sexes on day 0 at the mid- and high-dose levels. These effects were consistent with cholinesterase inhibition. At 650 mg/kg, the predominant clinical signs observed in both sexes on the day following dosing consisted of gait alterations (prostration, rocking, lurching, and swaying when ambulatory; walked on tiptoes), constricted pupils, tremors (fore- and hindlimb), cool body to the touch, yellow material on various body surfaces, red material on forelimbs, around eyes, nose, and mouth, and/or increased defecation. Several of these findings were noted in a limited number of rats (mainly females) on days 2, 3, 4, and/or 5. At 325 mg/kg, one female showed gait alterations and one male and 3 females had constricted pupils on day 1. The neuropathologic examination gave no indication of any dose-related permanent effects on the brain or in the peripheral or central nervous tissues, consistent with the lack of permanent changes in muscular coordination and/or behavior.

The NOAEL is 65 mg/kg, and the LOAEL is 325 mg/kg, based on transient neurotoxic effects in both sexes on day 0.

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for an acute neurotoxicity study in rats (OPPTS 870.6200, OECD 424).

### 870.6200b Subchronic Neurotoxicity Screening Battery - Rat

In a subchronic neurotoxicity study (MRID 43294101), tetrachlorvinphos (99% a.i.; Lot #01-KMJ-012) was administered via the diet to 10 Sprague-Dawley Crl:CD®BR rats for 90 days at dose levels of 0, 200, 1000, or 5000 ppm. A Functional Operational battery (FOB) and motor activity were assessed at weeks -1, 0, 3, 7, and 12.

There were no deaths or clinical signs of toxicity. There were no measurement of cholinesterase activity, but cholinergic signs were not observed. Decreased body weight was observed throughout the study in males at 5000 ppm (8%-9%) and in females at 2000 ppm (8%-10%) and 5000 ppm (7%-13%). There were no indications of any dose-related effects during the home-cage, handling, open-field, sensory or neuromuscular observations. There were no significant dose-related differences between groups involving group mean motor activity counts. Brain weights and brain measurements (weight and morphometric) were comparable among the groups for both sexes, and there were no differences in histomorphological neurology findings between the control and 5000 ppm groups.

The NOAEL is 5000 ppm (250 mg/kg/day; standard conversion). The LOAEL was not identified.

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for a subchronic neurotoxicity study in rats (OPPTS 870.6200, OECD 424).

### 870.6300 Developmental Neurotoxicity - Rat

In a developmental neurotoxicity study (MRID 46660601), tetrachlorvinphos (99.6% a.i.; Lot #: NJ250RB08) in aqueous 1% (w/v) methylcellulose was administered via gavage (10 mL/kg) to pregnant Sprague-Dawley rats (25/dose) from gestation day (GD) 6 to lactation day (LD) 6 at doses of 0, 10, 50, or 200 mg/kg/day. Additionally, the $F_1$ pups were similarly dosed on postnatal days (PNDs) 7-21. Dams were allowed to deliver naturally and were sacrificed on LD 21. On PND 4, litters were standardized to 10 pups/litter; the remaining offspring and dams were sacrificed and subjected to a gross necropsy. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following subsets: Subset 1, PND 21 brain weights and neurohistological evaluations; Subset 2, water maze and passive avoidance test; Subset 3, motor activity and auditory startle habituation; Subset 4, terminal brain weights and neurohistological evaluations; and Subset 5, standardize litter size to ten pups (5 male and 5 female) per litter on PND 4-21.

In dams, there were no treatment-related effects on mortality, clinical signs, body weight, body weight gain, feed consumption, FOB, or gross pathology. No treatment-related effects on reproductive parameters were observed. **The maternal LOAEL was not observed. The maternal NOAEL was 200 mg/kg/day (HDT).**

In offspring, there were no treatment-related effects on viability, litter observations, clinical signs, body weight, food consumption, FOB, motor activity, acoustic startle habituation, learning and memory (passive avoidance and water maze), gross pathology, or histopathology parameters.

At 200 mg/kg/day, decreases ($p \leq 0.05$) in body weight were noted in the males (↓5-8%) on PNDs 15 and 16 (pre-weaning) and PND 22 (post-weaning) and in the females (↓6%) on PND 29 (post-weaning). Body weight gains were decreased ($p \leq 0.05$) during pre-weaning at several intervals in the males (↓12-28%) and females (↓13-26%). Decreases ($p \leq 0.05$) in body weight gains during post-weaning were observed in the males on PNDs 21-22 (↓36%) and in the females on PNDs 21-22 and 22-29 (↓7-28%). Absolute brain weight was decreased ($p \leq 0.01$) by 8% in the males. This finding was judged to correlate with the treatment-related decreases ($p \leq 0.05$) in several microscopic linear brain measurements: (i) thickness of the striatum on PND 21 (↓4-5% both sexes) and PND 70 (↓7% males only); (ii) thickness of the corpus callosum on PND 70 (↓16-21% both sexes); (iii) thickness of the hippocampal gyrus on PND 70 (↓7-9% both sexes); and (iv) height of the cerebellum on PND 70 (↓7% males only). It is noted that on PND 21, decrease in single morphometric parameter was seen in both sexes with the small magnitude (4-5%) whereas on PND 70, decrease in multiple morphometric measurements were seen in both sexes with greater magnitude (7-21%) than that seen in PND 21.

No treatment related effects were noted in the ≤50 mg/kg/day $F_1$ offspring.

**The offspring LOAEL was 200 mg/kg/day, based on decreases in body weight, body weight gains and several morphometric linear brain measurements in both sexes, and decreased absolute brain weight in the males on PND 70. The offspring NOAEL was 50 mg/kg/day.**

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6; OECD 426) in the rat.

## A.4.8 Metabolism

### 870.7485 Metabolism – Rat

In a metabolism study (MRID 41988401), single oral doses of $^{14}C$-tetrachlorvinphos (97%; Lot # 2587-180; $^{14}C$ in the phenyl group) were administered *via* gavage to three groups of Sprague-Dawley rats (5/sex) at (A) 5 mg/kg, (B) 5 mg/kg following 14 consecutive doses of unlabeled test material, or (C) 250 mg/kg, and urine (0-8 hours, 8-24 hours, and at 24-hour intervals up to 120 hours post dose) and feces (at 24-hour intervals up to 120 hours post dose) were collected. At 120 hours post dose, the rats were sacrificed, and whole blood/plasma, heart, lungs, liver, kidney, spleen, gastrointestinal tract, brain, ovaries/testes, total skin, and samples of muscle, fat, and bone, and the remaining carcass were collected for analysis.

Most of the radioactivity was recovered in urine (46%-60%) and feces (38%-56%) within 48 hours post dose. The greatest activity in the urine was found in the 0-8 hour interval for both sexes following the single and repeat 5 mg/kg dose, whereas the greatest activity following the 250 mg/kg dose was found in the 8-24 hour interval. Following the single 250 mg/kg dose, males excreted a similar % (≈50%) of the dose *via* the urine and feces, whereas the females excreted the majority *via* the urine (70% vs 30%). Following the single 5 mg/kg dose, males excreted 60%



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*via* the urine and 40% via the feces, and females excreted equal amounts (≈50%) *via* the urine and feces. Following the 14-day dosing period, both sexes excreted approximately equal amounts (≈50%) *via* the urine and feces. Only minor amounts (<0.5%) of the radiolabel were recovered from tissues after 5 days, with the GI tract, whole blood, and lungs showing the highest concentrations. The major metabolite in urine was trichloromandelic acid (18%-26%), and the major metabolite in feces was trichlorophenylethanol (>13%). Since the oral LD50 for female rats is lower than the male LD50, it is noteworthy that males of all groups excreted more total label as trichloromandelic acid, a more completely metabolized form of TCVP, whereas the high-dose females tended to excrete more of the label as desmethyl TCVP (with the phosphate group still attached to the remainder of the molecule), a compound that could be derived from TCVP with only a single metabolic step.

The metabolism study is classified as Acceptable/Guideline, and it satisfies the guideline requirement for a metabolism study (OPPTS 870.7485, OECD 417) in rodents.

#### 870.7600 Dermal Penetration Study – Rat

In a dermal absorption study (MRID 42111501), male CD rats (28/group/time point) were exposed dermally to doses of 0.01, 0.1, 1 or 5 mg/cm$^2$ radiolableled tetrachlorvinphos (97% a.i.), with some of each dose group sacrificed at 0.5, 1, 2, 4, or 10 hours. Additionally, there was a group of animals, sacrificed at 72 hours, in which the skin was washed at 10 hours. The area of the dermal application was washed to recover unabsorbed tetrachlorvinphos. Then, the skin, urine, feces, and carcass were analyzed for percent of total tetrachlorvinphos applied. For the group sacrificed at 10 hours, 84 % of the total tetrachlorvinphos applied (0.1 mg/cm$^2$) was recovered in the wash, and 9.57 % was in the skin, urine, feces, and carcass. The percent absorption increased with duration of exposure and generally decreased with increasing dose. The actual quantity of tetrachlorvinphos absorbed increased with increasing dose.

This study is classified as **Acceptable/Guideline**, and it satisfies the guideline requirement (OCSPP 870.7600) for a dermal penetration study in the rat.

### A.4.9 Immunotoxicity

#### 870.7800

In an immunotoxicity study (MRID # 48794701), Tetrachlorvinphos [100.05%, lot #100113] was administered to Crl:CD-1(ICR) female mice (10/dose) via oral gavage at dose levels of 0, 75, 300, or 1200 mg/kg/day for 28 consecutive days. An additional group of 10 positive control females received cyclophosphamide 10 mg/kg/day via gavage for 28 days. On Day 25 a single intravenous (IV) dose of 0.25 mL/animal of sheep red blood cells (SRBC) 2x10$^8$ cells/animal was administered to all animals. During the study, clinical signs, morbidity and mortality, bodyweight, food consumption, water consumption were measured and evaluated. On Day 29, blood samples were collected from the orbital sinus under isoflurance anaesthesia. Animals were euthanized

with carbon dioxide followed by exsanguination. All animals were subject to a complete necropsy examination. Spleen and thymus weights were recorded and immunotoxicity investigations by an Enzyme-linked immunosorbent assay (ELISA).

There were no treatment-related clinical signs and no unscheduled deaths. There were no treatment-related effects on body weights, food or water consumption. There were no treatment related necropsy findings. Absolute and relative mean thymus weight were statistically significantly lower ($p<0.05$) at 300 mg/kg/day group when compared with the vehicle control group. There were lower mean absolute thymus weight at 1200 mg/kg/day but it was not statistically significant; and there was no dose-dependent response in treated groups. Spleen weights in treated groups were not significantly different from the vehicle control group.

**For systemic toxicity, the NOAEL is 1200 mg/kg/day, the LOAEL was not established.**

When compare to the vehicle control group, the low and mid dose groups (75 and 300 mg/kg/day) had slightly higher anti-SRBC IgM levels, and the highest dose group (1200 mg/kg/day) had lower IgM levels. However, there were no statistically significant treatment-related effects on the specific anti-SRBC antibody response. High inter-individual variability was noted in all the treatment groups as well as in the control group. Evaluation of the individual animal data of this study did not show any trend or distribution that would demonstrate significant suppression of anti-SRBC IgM response. Animals in positive control group showed a statistically significant ($p< 0.05$) decrease of the anti-SRBC IgM response. This confirmed the ability of the test system to detect immuno-suppressive effects and confirmed the validity of the study design.

The NK cells activity assay was not performed. The toxicology database for tetrachlorvinphos does not reveal any evidence of treatment-related effects on the immune system. The overall weight of evidence suggests that this chemical does not directly target the immune system. Under HED guidance, a NK cells activity assay is not required at this time.

**For immunotoxicity, the NOAEL is 1200 mg/kg/day, tested above the limit dose; the LOAEL was not established.**

This immunotoxicity study is classified **acceptable/ guideline**, and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in mice.

## Special Studies

### Comparative Cholinesterase Studies

A series of studies (acute, repeat, gestational) was performed to investigate the effect of TCVP on brain and blood cholinesterase (ChE) activity and to determine the peak time of ChE

inhibition following both acute and repeated dosing in pre-weaning, young, maternal, and adult Sprague Dawley rats.

**Comparative Cholinesterase Assay - Repeat (11-days) Dose**:

In a comparative cholinesterase study (2012, MRID No.: 48773401), five groups of 10/sex of both 11 day old and young adult (~61 days) Crl:CD(SD) strain rats were dosed *via* gavage at dose levels of 0, 5, 10, 50 or 200 mg/kg/day of tetrachlorvinphos (TCVP) in methylcellulose. After 11 doses, the rats were sacrificed and assessed for red blood cell (RBC) and brain cholinesterase (ChE) activity.

*Systemic effects.* One female pup in the high dose group died after only two doses and its death was attributed to treatment. There was some decrease in body weight in this rat pup prior to death and the appearance was described as moderately dehydrated but no signs of typical ChE inhibition toxicity were reported. No other pups demonstrated clinical signs. There was an initial negative body weight gain in the adult males (days 1-2) but no clinical signs were evident in the adults.

**The LOAEL for systemic effects for both ages is 200 mg/kg/day, based on a single death of a female pup. The NOAEL is 50 mg/kg/day.**

*RBC ChE inhibition.* Adult males demonstrated a statistically significant reduction (13.3%) in RBC ChE level at 10 mg/kg/day. At 50 mg/kg/day, both male pups and adults had similar levels of inhibition (30% to 33%). At 200 mg/kg/day, the male pups were inhibited more (59.9%) than the male adults (36.3%). At 50 mg/kg/day, adult females demonstrated more inhibition (40.6%) than the female pups (19.2%) but at 200 mg/kg/day both female pups and adults had ~62% inhibition.

**The LOAEL for RBC ChE inhibition is 50 mg/kg/day for both sexes and both ages. The NOAEL is 10 mg/kg/day.**

*Brain ChE.* There was a dose-related decrease in brain ChE in adult females that was statistically significant at 10 mg/kg/day (↓12.2%), 50 mg/kg/day (↓42%), and 200 mg/kg/day (↓57.2%). Both sexes of pups displayed similar levels of brain ChE inhibition at 50 mg/kg/day (males ↓15.7%/females ↓18.7%) and 200 mg/kg/day (males ↓46.3%/females ↓45.1%), which were statistically significant. The adult males displayed statistically significant brain ChE inhibition at 50 mg/kg/day (↓14.9%) and 200 mg/kg/day (↓17.8%), although the magnitude of the response was similar at both dose levels.

**The LOAEL for brain ChE inhibition is 10 mg/kg/day, based on significant inhibition in adult females. The NOAEL is 5 mg/kg/day in adult females. The LOAEL for brain ChE inhibition is 50 mg/kg/day in male and female pups and in male adults. The NOAEL in male and female pups and in male adults is 10 mg/kg/day.**



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*Overall conclusion.* The main objective of this study was to determine if the pups are more sensitive than the adults to the cholinesterase inhibitory potential of TCVP. A comparison of the magnitude of cholinesterase inhibition in the brain and RBC compartments in the females shows the female pups with less inhibition (at 50 mg/kg/day) or a comparable amount of inhibition (at 200 mg/kg/day) as the female adults. For the males, a similar magnitude of inhibition was displayed in the pups and adults at 50 mg/kg/day, although the male pups displayed a greater % inhibition in both compartments at 200 mg/kg/day than the adult males. Based on assignment of the NOAEL and LOAEL, there was no demonstration for increased sensitivity of the pups relative to the adults for either RBC or brain ChE. Although the magnitude of brain inhibition in the male pups was greater than in the male adults, this occurred only at the 200 mg/kg/day dose level. The benchmark dose analysis of the brain cholinesterase data does not show the male pups to be more sensitive.

A benchmark dose analysis of the repeat dose cholinesterase data (RBC and brain) was performed that provides both the $BMD_{10}$ and $BMDL_{10}$ of adults and PND11 pups.

| **$BMD_{10}$s and $BMDL_{10}$s for Adult Rat and PND 11 Pup Cholinesterase** | | | | |
|---|---|---|---|---|
| | **RBC $BMD_{10}$** | **RBC $BMDL_{10}$** | **Brain $BMD_{10}$** | **Brain $BMDL_{10}$** |
| Adult males | 7.7178 | 3.5942 | 33.803 | 24.4489 |
| Adult females | 8.6762 | 6.1335 | 7.1764 | 5.4980 |
| PND 11 males | 20.4688 | 15.9719 | 33.4825 | 26.5707 |
| PND 11 females | 20.5608 | 13.1692 | 24.2224 | 18.9412 |

***Classification:*** The classification of this repeat dose *in vivo* comparative cholinesterase inhibition study is Acceptable/Non-Guideline. It does not satisfy a guideline requirement. It satisfies the generic data call-in requirement for TCVP for a comparative cholinesterase study in adult rats versus postnatal day (PND) 11 rat pups.

**Comparative Cholinesterase Assay - Acute Dose**

In an acute comparative cholinesterase study (MRID 48773401a), TCVP (98.99% a.i.; Batch # TX100405)] was administered to 10 Crl:CD (SD) adult rats/sex/dose, 10 Crl:CD (SD) postnatal day (PND) 11 pups/sex/dose, and 10 Crl:CD(SD) PND 21 pups/sex/dose once *via* gavage (10 mL/kg) at dose levels of 0 (1% w/v aqueous methylcellulose), 10, 50, 150, or 300 mg/kg. Viability, clinical signs, body weights, and brain weights were evaluated. Approximately three hours post dose, red blood cell (RBC) and brain acetylcholinesterase (AChE) levels were determined.

There were no treatment-related deaths. Treatment-related clinical signs included soft or liquid feces in several adult males at 150 mg/kg and 300 mg/kg, decreased motor activity in PND 21 males and females at 150 mg/kg and 300 mg/kg, and urine-stained abdominal fur in PND 21 rats at 300 mg/kg. There were no clinical signs in the PND 11 pups or adult females.

Cholinesterase inhibition was displayed in both compartments in all age groups at all dose levels, with one exception. The magnitude of the response in the adult female rats (RBC and brain) was lower than in the adult male rats and in both sexes of PND 11 and PND 21 pups.

For both compartments, the magnitude of the response was comparable among the age groups and similar between the sexes, with the exception of the adult female rats. *All groups showed a similar response in both the RBC and brain cholinesterase compartments at each dose level.*

**The NOAEL for adult rats (both sexes) for RBC and brain cholinesterase inhibition following an acute oral dose was not determined. The LOAEL for adult rats is 10 mg/kg.**

**The NOAEL for PND 21 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 21 pups is 10 mg/kg.**

**The NOAEL for PND 11 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg.**

This comparative study of RBC and brain cholinesterase activities following acute oral treatment with TCVP in adult and neonatal (PND 11 and PND 21) rats is classified **Acceptable/Non-guideline.** It does not satisfy any guideline requirement; however, it does satisfy the data requirement for TCVP for an acute comparative cholinesterase activity between adult and young rats.

**COMMENT**: This acute exposure comparative cholinesterase study final report was embedded within the repeat dose comparative cholinesterase study report (MRID 48773401); it should have been submitted as a separate study report and been given a unique MRID #. The results of the Benchmark dose analysis for the acute study are provided below.

| TCVP/Study | Sex/Age | Compartment | BMD Results (mg/kg) | |
|---|---|---|---|---|
| | | | $BMD_{10}$ | $BMDL_{10}$ |
| MRID 48773401a Acute CCA | Male PND11 | Brain | 5.1 | 4.5 |
| | Female PND11 | Brain | 5.9 | 4.8 |
| MRID 48773401a Acute CCA | Male PND11 | RBC | 5.0 | 4.1 |
| | Female PND11 | RBC | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | Male PND21 | Brain | 3.5 | 3.2 |
| | Female PND21 | Brain | 5.3 | 3.7 |
| MRID 48773401a Acute CCA | Male PND21 | RBC | 3.2 | 2.8 |
| | Female PND21 | RBC | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Male Adult | Brain | 7.4 | 5.6 |
| | Female Adult | Brain | 11.6 | 9.8 |
| MRID 48773401a | Male Adult | RBC | 6.5 | 3.6 |

| | | | | |
|---|---|---|---|---|
| Acute CCA | Female Adult | RBC | 14.9 | 11.2 |

**Comparative Cholinesterase Assay - Gestational Exposure**

In a maternal and fetal exposure study (2010, MRID 48291101), tetrachlorvinphos (TCVP) (purity 99.6%, Lot No. NJ250RB08) dissolved in 1% aqueous (w/v) methylcellulose was administered to pregnant female Crl:CD(SD)IGS BR VAF/Plus rats via gavage once daily on days 6 through 21 of gestation at doses of 0, 75, 150 or 300 mg/kg/day. On gestation day 21 (GD 21), within 2 hr of the last dose, whole blood samples and brains were collected from the dams for cholinesterase (ChE) assessment. Dams were Caesarean-sectioned and pooled fetal blood samples and brains were collected for ChE assessment.

***Maternal Systemic and Litter Effects:*** All dams survived until scheduled sacrifice and no adverse clinical observations were reported. No Caesarean-sectioning or litter parameters were affected. Body weight *gains* and food consumption in dams were reduced in the 150 and 300 mg/kg/day groups. No gross lesions were observed during necropsy of the dams. There were no fetal gross external alterations and fetal body weights, brain absolute and relative weights were comparable among the dose groups. Since the main purpose of this study was to assess differential sensitivity between the dams and the fetuses, no assignment of a NOAEL and LOAEL for maternal systemic and litter effects is being made.

***RBC ChE***: Neither the dams nor the fetuses demonstrated RBC ChE inhibition. In dams the values were 5.1%, 15% and 3% lower than the control for the low, mid and high doses, respectively. Interpretation of the fetal RBC data was confounded because only 1 or two samples were available and no sample was available for the mid dose group. *The RBC ChE data are considered unacceptable because the repeat dosing study (2012, 48773401) conducted in the same laboratory in the same strain of rat was clearly able to demonstrate RBC ChE inhibition at 50 and 200 mg/kg/day in females. There was no way to compare adult and fetal RBC ChE.*

***Plasma ChE***. Plasma ChE inhibition in dams was dose dependent being 62%, 71% and 77% for the low, mid and high dose groups, respectively. Fetal plasma ChE values were 22%, 18.5% and 20.8% less than the control for the low, mid and high dose groups, respectively. The lack of a dose response raises the question as to whether these lower values are actually inhibition. However, there is no indication that the fetuses are more sensitive than the dams for this compartment.

***Brain ChE.*** Brain ChE inhibition was also dose dependent in dams; *i.e.*, 31%, 44% and 67% for the low, mid and high doses, respectively. Fetal brain ChE values were 10%, 20.9% and 20.8% lower than the controls for the low, mid and high dose groups, respectively. Similar to the plasma ChE data, there is no dose response to support a conclusion that these lower values are actually inhibition. However, there is no indication that the fetal brain ChE is more sensitive to inhibition by TCVP than the dams.

This *in vivo* comparative ChE study is classified as **Acceptable/non-guideline**. The study does not satisfy a guideline requirement. It satisfies a data call-in-requirement for TCVP for a gestational comparative ChE study in maternal rats versus fetal rats, although it is to be noted that the dose levels selected are way too high. However, from the data available, no increase in sensitivity was evident. RBC ChE inhibition was not demonstrated in the dams or fetuses (no data), and the flat dose response curves for the brain ChE in both pups and adults confound the interpretation of the study. However, no additional gestational CCA study is being requested at this time because there is no indication that the fetuses were more affected than the dams.

**Comparative Cholinesterase Assay - Acute Exposure**

In an acute relative cholinesterase (ChE) sensitivity study (2010, MRID 48294601), tetrachlorvinphos (TCVP) (purity 99.6%, Lot No. NJ250RB08) was administered at doses of 0, 75, 150 or 300 mg/kg body weight dissolved in 1% aqueous (w/v) methylcellulose to Crl:CD(SD)IGS BR VAF/Plus strain young adult (about 42 days old) and to postnatal day (PND) 11 and 21 neonatal rats via a single oral (gavage) dose. Four rats/sex/dose were sacrificed on pretest and at 1, 2, 3, 4, 8 and 24 hours after dosing.

***Systemic effects.*** All pups and all adult rats groups survived. There were no adverse clinical or necropsy observations related to the TCVP administration, and no effects on body or brain weights were reported. Since this is a short term study primarily designed to assess for comparative sensitivity to ChE inhibition, no NOAEL or LOAEL for systemic effects will be assigned.

***General comments on ChE assessment.*** Only four rats/sex were available for assessment at each of the seven assessment times. Many of the RBC and plasma ChE assessments were made on only 0 (no sample available), 1, 2, or 3 samples because of loss of sample. In addition, duplicate samples that did not replicate contributed to the low number of sample to provide a meaningful mean. Brain ChE also appeared to be affected by the low number of samples. The results for all three enzyme sources indicated that there was inhibition at all doses but there was poor dose response with the degree of apparent inhibition at the higher doses often less that at the low dose of 75 mg/kg/day. There was also a lack of temporal concordance with high apparent inhibition at one time, a much lower degree at the following time and back to the higher level at the next time point. Another problem is that there was more or similar apparent inhibition at the low dose of 75mg/kg in this acute study than there was in the repeat dosing studies (2012, MRID 48773401, eleven daily doses) at 200 mg/kg/day and in the gestational study (2010, MRID 48291101, fifteen daily doses) at 150 mg/kg/day. Also, the repeat dosing study clearly indicated that there was no increase in sensitivity of the pups relative to the adults with regard to potential inhibition by TCVP. In this acute study, there were several comparisons among the PND11, PND21 and adults that suggested the pups were more sensitive.

Overall, there is little confidence in the data mainly because of the lack of clear dose and temporal responses.

***Benchmark Dose (BMD) modeling.*** BMD modeling was performed but could not be done with the RBC data or for the PND11 brain data because of too few samples and/or the data would not otherwise fit the models. BMD modeling for the brain data (for the three hour assessment time) indicated that for males, the adults may be slightly more sensitive than the PND 21 pups but the females were considered similar with respect to the $BMD_{10}$ and $BMDL_{10}$.

| **TCVP/Study** | **Sex/Age** | **Compartment** | **BMD Results** (mg/kg/day) | |
|---|---|---|---|---|
| | | | **$BMD_{10}$** | **$BMDL_{10}$** |
| MRID 48294601 Acute CCA | Adult male | Brain | 6.76716 | 5.02249 |
| MRID 48294601 Acute CCA | Adult female | Brain | 11.2932 | 4.55107 |
| MRID 48294601 Acute CCA | Male pup PND 21 | RBC | 16.8647 | 9.71265 |
| MRID 48294601 Acute CCA | Female pup PND 21 | Brain | 9.80073 | 4.6942 |
| MRID 48294601 Acute CCA | Male pup PND 21 | Brain | 11.246 | 6.76389 |

This study is classified as A**cceptable/Non-Guideline.** The study does not satisfy a guideline requirement. It satisfies a data call-in-requirement for TCVP for an acute comparative ChE study in adult, PND 21, and PND 11 pups, although there is too much variability in the data to make meaningful comparisons for sensitivity for RBC. Brain ChE data also had problems with variability and dose response to compare for sensitivity. However, from the data available, there is no conclusive evidence of increased sensitivity. No additional acute CCA study is being requested at this time because there is no indication that the young animal was more affected than the adult. NOTE: An additional acute comparative cholinesterase study (MRID 48773401a) was located and is discussed above.

## Appendix B. Results for BMD/BMDL modeling for TCVP

### B.1. Summary of OPP's ChE Policy & Use of BMD Modeling

OPP's AChE policy (USEPA, 2000[11]) describes the manner in which AChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or cholinesterase (ChE) inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung etc) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and RBC) ChE. Blood measures do not represent the target tissue, per se, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.

Refinements to OPP's use of AChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often the decreasing exponential empirical model has been used.

OPP does not have a defined BMR for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the $BMD_{10}$ is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the $BMD_{10}$.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity in the brain compartment and is a response level close to the background brain AChE level. With respect to biological considerations, a change in 10% brain AChE inhibition is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC AChE inhibition, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC AChE inhibition but BMRs up to 20% could be considered on a case by case basis as long as such PODs are protective for brain AChE inhibition, potential peripheral inhibition, and clinical signs of neurotoxicity.

## B.2. Summary Tables of Benchmark Dose (BMD) Analyses

BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using an exponential model for continuous data (Bever and Holman, D435480, 9/1/2016). The data selected for evaluation consisted of decreased brain and red blood cell (RBC) cholinesterase (AChE) activities from rats in an acute comparative cholinesterase assay (CCA; MRID 48773401a). The results of the acute dosing BMD analyses are summarized below in Table B.1.

**Table B.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on TCVP, Acute Oral Dosing Study in Rats.**

| Study | Age Sex | Brain $BMD_{10}$ | Brain $BMDL_{10}$ | RBC $BMD_{10}$ | RBC $BMDL_{10}$ |
|---|---|---|---|---|---|
| MRID 48773401a Acute CCA | PND 11 Male | 5.1 | 4.5 | 5.0 | 4.1 |
| MRID 48773401a Acute CCA | PND 11 Female | 5.9 | 4.8 | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | PND 21 Male | 3.5 | 3.2 | 3.2 | 2.8 |

| | | | | | |
|---|---|---|---|---|---|
| MRID 48773401a Acute CCA | PND 21 Female | 5.3 [a] | 3.7 | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Adult Male | 7.4 | 5.6 | 6.5 | 3.6 |
| MRID 48773401a Acute CCA | Adult Female | 11.6 [a] | 9.8 | 14.9 | 11.2 |

CCA = Comparative Cholinesterase Assay

[a]Although the model chosen resulted in program warning that "the model may not adequately describe the data", fit was considered adequate based on similarity to values from other data sets, plausibility after considering empirical data (ground-truthing), and visual assessment of the fit.

Previously, Benchmark Dose (BMD) analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using an exponential model for continuous data [2]. The Hill model was also performed for some data sets, but did not result in the best fit for the data. The data selected for evaluation consisted of decreased brain and red blood cell (RBC) cholinesterase (ChE) activities. Data were analyzed from a 21-day oral toxicity study (MRID 45570601), a 13-week subchronic oral toxicity study (MRID 43371201), a 2 year chronic oral toxicity study (MRID 42980901); a gestational comparative cholinesterase assay (MRID 48291101); and a 28-day inhalation toxicity study (MRID 48803501). The results of the repeated oral and inhalation dosing BMD analyses are summarized below in Table B.2. Good model fit ($p>0.1$) was obtained for the majority of the analyses, with any exceptions being noted.

| Table B.2. Results of BMD Exponential Modeling for Brain and RBC ChE Data on TCVP, Repeated Oral Dosing Studies in Rats, Ranging in Duration from 21 days to 2 years. | | | | |
|---|---|---|---|---|
| **TCVP Study** | **Age/Sex** | **Compartment** | **BMD Results** | |
| | | | **$BMD_{10}$** | **$BMDL_{10}$** |
| MRID 43371201 13W Oral – 13 Weeks | Adult Male | Brain | No dose response (analysis not performed) | |
| | Adult Female | Brain | No dose response | |
| | Adult Male | RBC | 61.6 mg/kg/day | 26.3 mg/kg/day |
| | Adult Female | RBC | 10.5 mg/kg/day | 8.0 mg/kg/day |
| MRID 42980901 Chronic Oral Tox – 364, 539, and 721 Days | Adult Female | RBC | No dose-response effect was observed at 364, 539, or 721 days | |
| MRID 45570601 21D Oral Tox – 21 Days | Adult Female | Brain | 14.7 mg/kg/day | 12.2 mg/kg/day |
| | | RBC | 9.9 mg/kg/day | 6.7 mg/kg/day |
| MRID 48803501 28D Inhalation – 28 Days | Adult Male | RBC | 0.122 mg/L | 0.022 mg/L |
| | Adult Female | RBC | 0.394 mg/L | 0.050 mg/L |

[1] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.
[2] J. Bever. Tetrachlorvinphos: Benchmark Dose Analysis of Subchronic and Chronic Studies to Support Derivation of Points of Departure. 5/20/2014. TXR # 0056970. D420286.

## Appendix C. Methodologies for HEC Calculations

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (e.g., systemic vs. portal-of-entry) and the pharmacokinetic (PK) **but not pharmacodynamic** (PD) differences between animals and humans. Based on the EPA's RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (e.g., systemic vs. portal-of-entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (e.g., acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid. These assumptions, in turn, vary depending on the type of toxicity observed. Thus the derivation of a HEC for inhaled gases is described by the following equation:

$$HEC = POD_{study} * \frac{D_{\text{animal exposure (hrs / day)}}}{D_{\text{human exposure (hrs / day)}}} * \frac{W_{\text{animal exposure (days / wk)}}}{W_{\text{human exposure (days / wk)}}} * RGDR$$

Where:
$POD_{study}$: Point of departure identified in the critical toxicology study
$D_{\text{animal exposure}}$: Duration of animal exposure (hrs/day; days/wk)
$D_{\text{anticipated exposure}}$: Anticipated human duration of exposure (hrs/day; days/wk)
RGDR: Regional Gas Dose Ratio

Calculations used to estimate the inhalation risk to humans from aerosols are dependent not on the RGDR as for gases, but on the regional deposited dose ratio (RDDR). Inhalation studies using aerosols characterize particulate exposure by defining the particulate diameter (mass median aerodynamic diameter [MMAD]) and the geometric standard deviation ($\sigma_g$), which is then used to determine the RDDR. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the rth region or target tissue.

$$RDDR_r = \frac{(RDD_r/\text{Normalizing Factor})_A}{(RDD_r/\text{Normalizing Factor})_H}$$

As with calculations for gases, the r regions and potential target tissues are the three respiratory regions (ET, TB, PU). The RDDR is easily calculated by using a software program designed specifically for computing the RDDR from the MMAD and $\sigma_g$ defined from an aerosol inhalation study. The values for the species-specific parameters used to calculate the RDDR are



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provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry."

**Regional Deposited Dose Ratio (RDDR) for TCVP**

MMAD = 2.57
Sigma g = 3.79

| SPECIES | Body Weight (g) | Minute Ventilation (VE, ml) |
|---|---|---|
| rat | 267 | 189.8 |
| human | 70000 | 13800.0 |

| | Extrarespiratory BW (g) | deposited fraction |
|---|---|---|
| rat | 267 | 0.460 |
| human | 70000 | 0.657 |
| RATIO | 0.004 | 0.700 |

RDDR = $(VE/BW)_{animal}/(VE/BW)_{human}$ * deposited $fraction_{animal}$/deposited $fraction_{human}$
= $(189.8/267)_{animal}/(13800/70000)_{human}$ * 0.460/0.657
= 2.525

The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the PK differences **but not the PD differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

***C.1. HEC Calculations for Residential Exposure:***

*Assume residents will be exposed for 24 hrs/day and 7 days/week:*

*HEC = $NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR*

*Residential Bystander HEC = 0.022 mg/L * (6/24) * (5/7) * 2.525 = 0.0099 mg/L*
*Residential Handler Outdoor HEC = 0.022 mg/L * 2.525 = 0.0555 mg/L*

| Table C.1.1. HEC Array for Residential Handler Risk Assessment. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 8 | 5 | 5 | 2.525 | 0.0555 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Table C.1.2. HEC Array for Residential Bystander Risk Assessment. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 24 | 5 | 7 | 2.525 | 0.099 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Key for Array Tables | |
|---|---|
| *LOAEL*: Lowest-observed adverse-effect level | *RRDR*: Regional Deposited Dose Ratio |
| *NOAEL*: No-observed adverse-effect level | *HEC*: Human-Equivalent Concentration |
| *Da*: Daily animal exposure (hrs/day) | *inter*: Interspecies extrapolation UF |
| *Dh*: Anticipated daily human exposure (hrs/day) | *intra*: Intraspecies variation UF |
| *Wa*: Weekly animal exposure (days/week) | *UF*: Other UF(s) |
| *Wh*: Anticipated weekly human exposure (days/week) | *ER:* Extra-respiratory effects |

***Route-to-Route Extrapolation***

*More information and details in: Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/98.*

*HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes. An activity factor is used to account for increased exposure resulting from increased respiration.*

*Using the HEC calculated (based on an increase in RBC cholinesterase inhibition in both sexes), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:*

*HED (mg/kg/day) = Dose (systemic HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg*

*Where:*

*A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route.*

*CF = conversion factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of J. Whalen and H. Pettigrew, 10/10/98).*

*D = duration; duration of daily animal or human exposure (hours).*

*AF = activity factor; animal default is 1. For humans the value varies with ventilation*

**11.8 L/hr/kg is the typical breathing rate assumed for humans.*

*Therefore, the residential HED for TCVP is calculated as follows:*

***Residential Handler HED:*** *(0.056 mg/L) x 11.8 L/hr/kg x 2 hr x 1 = 1.31 mg/kg/day*

***C.2. HEC Calculations Occupational Exposure:***

*Assume workers will be exposed for 8 hrs/day and 5 days/week:*

$HEC = NOAEL_{study} * (\text{daily duration of exposure}_{animal}/\text{daily duration of exposure}_{human}) * (\text{days/week of exposure}_{animal}/\text{days/week of exposure}_{human}) * RDDR$

Occupational - HEC = 0.022mg/L * (6/8) * (5/5) * 2.525 = 0.0416 mg/L.

**Table C.1.3. HEC Array for Occupational Risk Assessment.**

| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 8 | 5 | 5 | 2.525 | 0.0416 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Key for Array Tables | |
|---|---|
| *LOAEL*: Lowest-observed adverse-effect level | *RRDR*: Regional Deposited Dose Ratio |
| *NOAEL*: No-observed adverse-effect level | *HEC*: Human-Equivalent Concentration |
| *Da*: Daily animal exposure (hrs/day) | *inter*: Interspecies extrapolation UF |
| *Dh*: Anticipated daily human exposure (hrs/day) | *intra*: Intraspecies variation UF |
| *Wa*: Weekly animal exposure (days/week) | *UF*: Other UF(s) |
| *Wh*: Anticipated weekly human exposure (days/week) | *ER:* Extra-respiratory effects |



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**Route-to-Route Extrapolation**

More information and details in: Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/98.

HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral-equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes. An activity factor is used to account for increased exposure resulting from increased respiration.

Using the HEC calculated (based on an increase in RBC cholinesterase inhibition in both sexes), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:

HED (mg/kg/day) = Dose (systemic HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg

Where:

| | | |
|---|---|---|
| A | = | absorption; ratio of deposition and absorption in respiratory tract compared to absorption by the oral route. |
| CF | = | conversion factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of J. Whalen and H. Pettigrew, 10/10/98). |
| D | = | duration; duration of daily animal or human exposure (hours). |
| AF | = | activity factor; animal default is 1. For humans, the value varies with ventilation rates |

Therefore, the occupational HED for TCVP is calculated as follows:

**Occupational Handler HED:** 0.042 mg/L x 11.8 L/hr/kg x 1.0 x 8 hr = 3.94 mg/kg/day

Based on the current TCVP label, HED believes exposures can be short- (1-30) or intermediate- (1 to 6 months) term in duration. Long-term exposures are not anticipated for TCVP based on proposed labeled uses. For the short- and intermediate-term scenarios, inhalation data from the 28-day inhalation rodent study was most appropriate for determining HECs. In the RfC methodology, different HECs may be calculated for the same experimental NOAEL due to the following:

1. Different algorithms are used to derive HECs for systemic versus portal-of-entry effects. Typically, HECs are calculated separately for systemic versus portal-of-entry effect. For TCVP, extra-respiratory effects were observed and, therefore, only extra-respiratory HECs were derived.

Time adjustments are traditionally needed for non-occupational (bystander) versus occupational exposure scenarios. Traditionally, HECs for non-occupational exposure are based on the number of hours an individual may be at home. Therefore, the most conservative estimate of hours spent at home would be 24 hours/day and 7 days/week. In comparison, the average workweek for an occupational worker is 8 hours/day and 5 days/week. The HEC array table reflects the time adjustment in the calculations.



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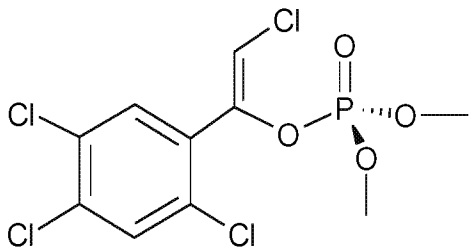
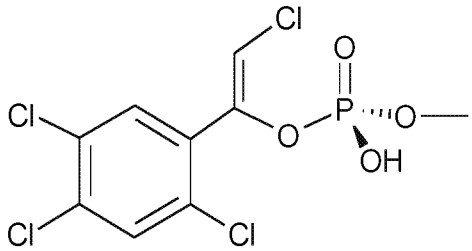
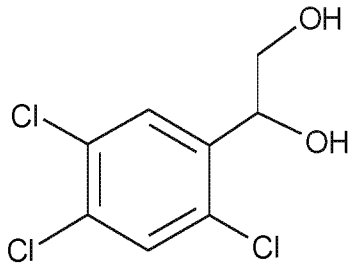
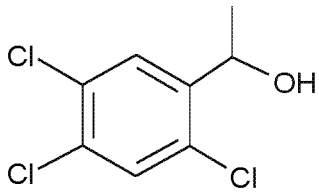
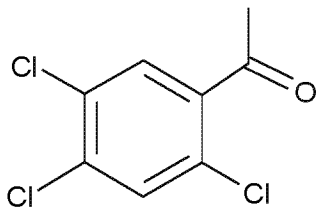
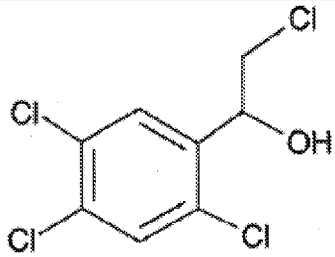
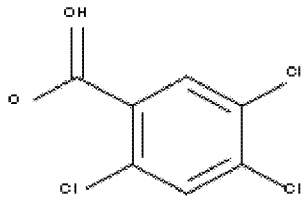
## Appendix D. Physical/Chemical Properties for Tetrachlorvinphos

| Table D.1 Physicochemical Properties of the Technical Grade Test Compound: Tetrachlorvinphos | | |
|---|---|---|
| Parameter | Value | Reference [1] |
| Melting point/range | 94.5 °C | (MRID 41222503) |
| pH | 5.5; 1% solution | (MRID 41222503) |
| Density | 0.83 g/mL | (MRID 41222503) |
| Water solubility | (25°C) 11.6 g/L | (MRID 41222503) |
| Solvent solubility | (mg/100mg at 25°C)<br>chloroform 80<br>methanol 21<br>acetone 44<br>hexane 0.8<br>toluene 28 | (MRID 41222503) |
| Vapor pressure | (25°C) 2.6 x $10^{-7}$ mm Hg | (MRID 41222503) |
| Dissociation constant, $pK_a$ | non-ionizable | (MRID 41222503) |
| Octanol/water partition coefficient, Log($K_{OW}$) | 3350 average $K_{OW}$ at 25 °C | (MRID 41222503) |
| UV/visible absorption spectrum | Not available | |

[1] Cited reference was reviewed under CB No. 7468, 4/3/91, R. Perfetti.

## Appendix E. TCVP and Metabolites

| Chemical Name | Structure | Physical/Chemical Properties[1] |
|---|---|---|
| **Tetrachlorvinphos**<br><br>IUPAC: (*Z*)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate<br><br>CAS: (*1Z*)-2-chloro-1-(2,4,5-trichlorophenyl)ethenyl dimethyl phosphate<br><br>CAS Reg. No. 22248-79-9<br><br>COP(=O)(OC)OC(=CCl)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 365.96 g/mol<br>VP: 2.6E-07 torr<br>Solubility: 11.6 mg/L<br>Log Kow: 3.53<br>Koc: 520-1100 L/$kg_{oc}$ |
| **Des-O-methyl tetrachlorvinphos**<br><br>IUPAC: (*Z*)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl methyl phosphate<br><br>CAS: (*1Z*)-2-chloro-1-(2,4,5-trichlorophenyl)ethenyl methyl phosphate<br><br>COP(=O)(O)OC(=CCl)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 351.94 g/mol<br>VP: 4.27E-08 torr<br>Solubility: 3.768 mg/L<br>Log Kow: 3.75<br>Koc: 702-827 L/$kg_{oc}$ |
| **1-(2,4,5-trichlorophenyl)ethanediol**<br><br>C(O)(CO)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 241.5 g/mol<br>VP: 4.37E-06 torr<br>Solubility: 250 mg/L<br>Log Kow: 2.37<br>Koc: 29-36 L/$kg_{oc}$ |
| **TCPEol (SD 15509, AA849)**<br><br>1-(2,4,5-trichlorophenyl)ethanol<br>1-(2,4,5-trichlorophenyl)ethan-1-ol<br><br>CC(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 225.5 g/mol<br>VP: 2.37E-04 torr<br>Solubility: 123 mg/L<br>Log Kow: 3.43<br>Koc: 319-359 L/$kg_{oc}$ |
| **TCPEone (CO300)**<br><br>2,4,5-trichloroacetophenone<br><br>CC(=O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 223.5 g/mol<br>VP: 6.32E-03 torr<br>Solubility: 27.4 mg/L<br>Log Kow: 3.61<br>Koc: 492-1,828 L/$kg_{oc}$ |

| Chemical Name | Structure | Physical/Chemical Properties[1] |
|---|---|---|
| **TCCEol (SD15125, AA576)**<br><br>l-(2,4,5-trichlorophenyl)-2-chloroethanol<br><br>C(Cl)C(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 260 g/mol<br>VP: 2.11E-05 torr<br>Solubility: 250 mg/L<br>Log Kow: 3.68<br>Koc: 494-608 L/$kg_{oc}$ |
| **TCBA (SD 15917)**<br><br>2,4,5-Trichlorobenzoic acid<br><br>C(=O)(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 225.5 g/mol<br>VP: 5.52E-04 torr<br>Solubility: 35.3 mg/L<br>Log Kow: 3.47<br>Koc: 157-166 L/$kg_{oc}$ |

1. Physical and chemical properties for degradates obtained through EPISuite 4.11.

## Appendix F. International MRLs and U.S. Tolerances

| Table F.1. Tetrachlorvinphos: Summary of U.S. and International Tolerances and Maximum Residue Limits. | | | | |
|---|---|---|---|---|
| Commodity | U.S. Tolerances, 40 CFR §180.252 [1] | | Codex MRL | Canada's MRL [2] |
| | Established U.S. Tolerance, ppm | Reassessed U.S. Tolerance, ppm | | |
| Milk, fat (reflecting negligible residues in whole milk) | 0.5 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | milk: 0.1 (of which not more than 0.04 ppm is tetrachlorvinphos *per se*) | None | None |
| Cattle and Hog, Fat | Fat of cattle and hog: 0.2 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | Fat of cattle and hog: 1.0 (of which not more than 0.8 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Muscle | meat of cattle and hog: 2.0 (of which not more than 2.0 ppm is tetrachlorvinphos *per se*) | meat of cattle and hog: 0.3 (of which not more than 0.2 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Kidney | kidney of cattle and hog: 1.0 (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | meat byproducts of cattle and hog : 1.0 (of which no more than 0.6 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Liver | liver of cattle and hog: 0.5 (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | | None | 1.5 [3] |

| Table F.1. Tetrachlorvinphos: Summary of U.S. and International Tolerances and Maximum Residue Limits. | | | | |
|---|---|---|---|---|
| Commodity | U.S. Tolerances, 40 CFR §180.252 [1] | | Codex MRL | Canada's MRL [2] |
| | Established U.S. Tolerance, ppm | Reassessed U.S. Tolerance, ppm | | |
| Cattle and Hog, Meat byproducts | meat byproducts, except kidney and liver of cattle and hog: 1.0 | | None | 1.5 [3] |
| Eggs | 0.2 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.3 (of which not more than 0.03 ppm is tetrachlorvinphos *per se*) | None | None |
| Poultry, muscle | meat of poultry: 3.0 (of which not more than 3.0 ppm is tetrachlorvinphos *per se*) | meat of poultry: 0.4 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, liver | 2.0 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | meat byproducts of poultry: 20 (of which not more than 6.0 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, meat byproducts | meat byproducts, except liver, of poultry: 2.0 | meat byproducts of poultry: 20 (of which not more than 6.0 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, fat | 7.0 (of which not more than 7.0 ppm is tetrachlorvinphos *per se*) | 1.4 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Apples | None | None | None | 10 |
| Grapes | None | None | None | 10 |

## Appendix G. Summary of Residential Handler Non-Cancer Exposures and Risks

| Table G.1. Residential Handler Non-cancer Dermal and Inhalation Dose Assuming a Liquid or Dust Formulation for Pet Collars. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal Dose (mg/kg/day)[3] | Inhalation Dose (mg/kg/day)[4] |
| Assume Liquid Formulation -- Use of Spot-On Exposure Data (based on 2012 Residential SOPs) | | | | | | | |
| Application of TCVP Collars | 2596-49: Cat | 120 | Negligible | 0.0036: 11 gram collar | 2 animals treated per day | 0.0012 | Negligible |
| | 2596-50, 62: Dog | | | 0.0061: 19 gram collar | | 0.0020 | |
| | | | | 0.010: 32 gram collar | | 0.0034 | |
| | 2596-63: Cat | | | 0.0048: 15 gram collar | | 0.0016 | |
| | | | | 0.0055: 17 gram collar | | 0.0018 | |
| | 2596-83: Cat | | | 0.0039: 12 gram collar | | 0.0013 | |
| | | | | 0.0080: 25 gram collar | | 0.0027 | |
| | 2596-84: Dog | | | 0.0061: 19 gram collar | | 0.0021 | |
| | | | | 0.010: 32 gram collar | | 0.0034 | |
| | 2596-139: Cat | | | 0.0032: 10 gram collar | | 0.0011 | |
| | 2596-139: Dog | | | 0.016: 50 gram collar | | 0.0054 | |
| | 11556-164: Dog | | | 0.0072: 24 gram collar | | 0.0024 | |
| | 11556-165: | | | 0.0045: | | 0.0015 | |

| Table G.1. Residential Handler Non-cancer Dermal and Inhalation Dose Assuming a Liquid or Dust Formulation for Pet Collars. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal Dose (mg/kg/day)[3] | Inhalation Dose (mg/kg/day)[4] |
| | Cat | | | 15 gram collar | | | |
| **Assume Dust Formulation -- Use of TCVP Dust Applicator Exposure Data (MRID 45519601)** | | | | | | | |
| Application of TCVP Collars | 2596-49: Cat | 1,700 | 3.1 | 0.0036: 11 gram collar | 2 animals treated per day | 0.017 | 0.00033 |
| | 2596-50, 62: Dog | | | 0.0061: 19 gram collar | | 0.029 | 0.00055 |
| | | | | 0.010: 32 gram collar | | 0.049 | 0.00092 |
| | 2596-63: Cat | | | 0.0048: 15 gram collar | | 0.023 | 0.00043 |
| | | | | 0.0055: 17 gram collar | | 0.026 | 0.00049 |
| | 2596-83: Cat | | | 0.0039: 12 gram collar | | 0.018 | 0.00035 |
| | | | | 0.0080: 25 gram collar | | 0.038 | 0.00072 |
| | 2596-84: Dog | | | 0.0061: 19 gram collar | | 0.029 | 0.00055 |
| | | | | 0.010: 32 gram collar | | 0.049 | 0.00092 |
| | 2596-139: Cat | | | 0.0032: 10 gram collar | | 0.015 | 0.00029 |
| | 2596-139: Dog | | | 0.016: 50 gram collar | | 0.076 | 0.00144 |
| | 11556-164: Dog | | | 0.0072: 24 gram collar | | 0.034 | 0.00065 |
| | 11556-165: Cat | | | 0.0045: 15 gram collar | | 0.021 | 0.00041 |

| Table G.2. Residential Handler Non-cancer Risk Estimates Assuming 1/99 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Reg. No.** | **Maximum Application Rate[1] (lb ai/pet)** | **Amount Handled Daily[2]** | **Combined 1/99 Liquid/Dust Dermal Dose (mg/kg/day)[3]** | **Combined 1/99 Liquid/Dust Inhalation Dose (mg/kg/day)[4]** | **Combined 1/99 Liquid/Dust Ratio Inhalation MOE[5]** |
| | | | | | | **LOC = 300** |
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0170 | 0.00032 | 4,100 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0285 | 0.00054 | 2,400 |
| | | 0.010: 32 gram collar | | 0.0481 | 0.00092 | 1,400 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0225 | 0.00043 | 3,100 |
| | | 0.0055: 17 gram collar | | 0.0255 | 0.00049 | 2,700 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0180 | 0.00034 | 3,800 |
| | | 0.0080: 25 gram collar | | 0.0376 | 0.00072 | 1,800 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0285 | 0.00054 | 2,400 |
| | | 0.010: 32 gram collar | | 0.0481 | 0.00092 | 1,400 |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0150 | 0.00029 | 4,600 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0751 | 0.00143 | 920 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0338 | 0.00064 | 2,000 |
| | 11556-165: Cat | 0.0045: 15 gram collar | | 0.0211 | 0.00040 | 3,300 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 1/99 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.01) + (Dust dermal dose * 0.99)

4 Combined 1/99 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.01) + (Dust dermal dose * 0.99)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 1/99 Liquid/Dust Inhalation Dose (mg/kg/day)

**Table G.3. Residential Handler Non-cancer Risk Estimates Assuming 50/50 Liquid/Dust Ratio Formulation Pet Collars.**

| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 50/50 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 50/50 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
|---|---|---|---|---|---|---|
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0092 | 0.00016 | 8,000 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0154 | 0.00028 | 4,800 |
| | | 0.010: 32 gram collar | | 0.0260 | 0.00046 | 2,800 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0122 | 0.00022 | 6,000 |
| | | 0.0055: 17 gram collar | | 0.0138 | 0.00025 | 5,300 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0097 | 0.00017 | 7,600 |
| | | 0.0080: 25 gram collar | | 0.0203 | 0.00036 | 3,600 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0154 | 0.00028 | 4,800 |
| | | 0.010: 32 gram collar | | 0.0260 | 0.00046 | 2,800 |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0081 | 0.00014 | 9,100 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0406 | 0.00072 | 1,800 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0183 | 0.00033 | 4,000 |
| | 11556-165: | 0.0045: | | 0.0114 | 0.00020 | 6,400 |

| Table G.3. Residential Handler Non-cancer Risk Estimates Assuming 50/50 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 50/50 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 50/50 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| | Cat | 15 gram collar | | | | |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 50/50 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.5) + (Dust dermal dose * 0.5)
4 Combined 50/50 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.5) + (Dust dermal dose * 0.5)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)

| Table G.4. Residential Handler Non-cancer Risk Estimates Assuming 99/1 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 99/1 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 99/1 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0014 | 3.27E-06 | 400,000 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0023 | 5.49E-06 | 240,000 |
| | | 0.010: 32 gram collar | | 0.0039 | 9.25E-06 | 140,000 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0018 | 4.33E-06 | 300,000 |
| | | 0.0055: 17 gram collar | | 0.0021 | 4.91E-06 | 270,000 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0015 | 3.47E-06 | 380,000 |
| | | 0.0080: 25 gram collar | | 0.0030 | 7.22E-06 | 180,000 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0023 | 5.49E-06 | 240,000 |
| | | 0.010: | | 0.0039 | 9.25E-06 | 140,000 |

| Table G.4. Residential Handler Non-cancer Risk Estimates Assuming 99/1 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 99/1 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 99/1 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| | | 32 gram collar | | | | |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0012 | 2.89E-06 | 450,000 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0061 | 1.44E-05 | 91,000 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0027 | 6.51E-06 | 200,000 |
| | 11556-165: Cat | 0.0045: 15 gram collar | | 0.0017 | 4.07E-06 | 320,000 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 99/1 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.99) + (Dust dermal dose * 0.01)
4 Combined 99/1 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.99) + (Dust dermal dose * 0.01)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| Application of TCVP Dusts/Powders | 47000-123: Dog | Inhalation: 300 | 1,700 | 3.1 | 0.00037: small | 2 animals treated per day | 0.0018 | N/A, No Dermal Hazard | 0.000034 | 39,000 |
| | | | | | 0.00094: medium | | 0.0044 | | 0.000084 | 16,000 |
| | | | | | 0.0015: large | | 0.0071 | | 0.00013 | 9,700 |
| | 47000-123: Cat | | | | 0.000094: small | | 0.00044 | | 0.0000084 | 160,000 |
| | | | | | 0.00023: medium | | 0.0011 | | 0.000020 | 65,000 |

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| | | | | | 0.00034: large | | 0.0016 | | 0.000030 | 43,000 |
| | 2596-78: Cat | | | | 0.00062: small | | 0.0029 | | 0.000056 | 24,000 |
| | | | | | 0.0010: large | | 0.0049 | | 0.000093 | 14,000 |
| | 2596-79; Dog | | | | 0.0010: small | | 0.0049 | | 0.000093 | 14,000 |
| | | | | | 0.0021: medium | | 0.0097 | | 0.00019 | 7,100 |
| | | | | | 0.0026: large | | 0.0122 | | 0.00023 | 5,600 |
| | 67517-82: Dog | | | | 0.0011: small | | 0.0053 | | 0.00010 | 13,000 |
| | | | | | 0.0028: medium | | 0.013 | | 0.00025 | 5,200 |
| | | | | | 0.0045: large | | 0.021 | | 0.00040 | 3,200 |
| | 67517-82: Cat | | | | 0.00028: small | | 0.0013 | | 0.000025 | 52,000 |
| | | | | | 0.00067: medium | | 0.0032 | | 0.000061 | 22,000 |
| | | | | | 0.0010: large | | 0.0048 | | 0.000091 | 14,000 |
| Application of TCVP Pump/Trigger Sprays | 2596-126, -140: Cat (Trigger) | | 820 | 3.3 | 0.00055: small | | 0.0013 | N/A, No Dermal Hazard | 0.000053 | 25000 |
| | | | | | 0.00077: medium | | 0.0018 | | 0.000074 | 18000 |
| | 2596-140 Cat (Pump) | | | | 0.00011: small | | 0.00026 | | 0.000011 | 120,000 |
| | | | | | 0.00016: large | | 0.00036 | | 0.000015 | 87,000 |

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| | 2596-125, -140: Dog (Trigger) | | | | 0.00077: small | | 0.0018 | | 0.000074 | 18,000 |
| | | | | | 0.00088: medium | | 0.0020 | | 0.000084 | 16,000 |
| | | | | | 0.0015: large | | 0.0035 | | 0.00015 | 8,900 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide)
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/pet) × Area Treated or Amount Handled (pets/day) × Dermal Absorption Factor (9.6 %) ÷ Body Weight (69 kg). Dermal dose presented only for purpose of calculation of cancer risks for residential handlers.
4 No dermal MOE estimated due to lack of dermal hazard.
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/pet) × Area Treated or Amount Handled (pets/day) ÷ Body Weight (69 kg).
6 Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## Appendix H. Summary of Residential Handler Cancer Exposure and Risk Estimates

**Table H.1. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 1/99 Liquid/Dust Formulation Approach.**

| Reg No./ Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | 1/99 Liquid/Dust Cancer Risk Estimate[3] |
|---|---|---|---|---|---|
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 2.2E-07 |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.7E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 6.3E-07 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 3.0E-07 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 3.3E-07 |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 2.4E-07 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 4.9E-07 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.7E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 6.3E-07 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 2.0E-07 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 9.8E-07 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 4.4E-07 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 2.8E-07 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.01) + (Dust LADD * 0.99)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table H.2. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 50/50 Liquid/Dust Formulation Approach**

| Reg No./ Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | 50/50 Liquid/Dust Cancer Risk Estimate[3] |
|---|---|---|---|---|---|
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 1.2E-07 |

| Table H.2. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 50/50 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 2.0E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 3.4E-07 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 1.6E-07 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 1.8E-07 |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 1.3E-07 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 2.7E-07 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 2.0E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 3.4E-07 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 1.1E-07 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 5.3E-07 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 2.4E-07 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 1.5E-07 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.5) + (Dust LADD * 0.5)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table H.3. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 99/1 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 1.8E-08 |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.0E-08 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 5.0E-08 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 2.3E-08 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 2.7E-08 |

| Table H.3. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 99/1 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 1.9E-08 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 3.9E-08 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.0E-08 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 5.0E-08 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 1.6E-08 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 7.8E-08 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 3.5E-08 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 2.2E-08 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.99) + (Dust LADD * 0.01)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table H.4. Residential Handler Dermal and Inhalation Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Total LADD[1,2]** | **Cancer Risk Estimate[3]** |
| **Dust/Powder** | | | | |
| 47000-123: Dog | Small | Adult | 1.9E-05 | 3.5E-08 |
| | Medium | | 4.7E-05 | 8.7E-08 |
| | Large | | 7.6E-05 | 1.4E-07 |
| 47000-123: Cat | Small | | 4.7E-06 | 8.7E-09 |
| | Medium | | 1.1E-05 | 2.1E-08 |
| | Large | | 1.7E-05 | 3.1E-08 |
| 2596-78: Cat | Small | | 3.1E-05 | 5.7E-08 |
| | Medium | | 5.2E-05 | 9.6E-08 |

| Table H.4. Residential Handler Dermal and Inhalation Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Total LADD[1,2]** | **Cancer Risk Estimate[3]** |
| 2596-79: Dog | Small | Adult | 5.2E-05 | 9.6E-08 |
| | Medium | | 1.0E-04 | 1.9E-07 |
| | Large | | 1.3E-04 | 2.4E-07 |
| 67517-82: Dog | Small | | 5.7E-05 | 1.0E-07 |
| | Medium | | 1.4E-04 | 2.6E-07 |
| | Large | | 2.3E-04 | 4.2E-07 |
| 67517-82: Cat | Small | | 1.4E-05 | 2.6E-08 |
| | Medium | | 3.4E-05 | 6.2E-08 |
| | Large | | 5.1E-05 | 9.4E-08 |
| **Pump/Trigger Sprays** | | | | |
| 2596-126: -140: Cat (Trigger) | Small | | 1.4E-05 | 2.5E-08 |
| | Large | | 1.9E-05 | 3.5E-08 |
| 2596-140: Cat (Pump) | Small | | 2.8E-06 | 5.1E-09 |
| | Large | | 3.9E-06 | 7.2E-09 |
| 2596-125, -140: Dog (Trigger) | Small | | 1.9E-05 | 3.5E-08 |
| | Medium | | 2.2E-05 | 4.0E-08 |
| | Large | | 3.9E-05 | 7.0E-08 |

1 Total Lifetime Average Daily Dose (LADD, mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
2 Dermal and Inhalation LADD equations provided in Appendix B.
3 Cancer risk estimates = Total LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

## Appendix I. Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates

**Table I.1. Residential Post-application Non-cancer Incidental Oral Dose Assuming a Liquid or Dust Formulation for Pet Collars.**

| Animal Type | Animal Size | Application Rate (mg ai) | $F_{ai hands}$ | DE<br>Dermal Exposure (mg) | $SA_H$<br>Surface area of 1 hand ($cm^2$) | HR<br>Hand residue loading ($mg/cm^2$) | $F_m$<br>Fraction of hand mouthed | ET<br>Exposure Time (hours/day) | Replenish-ment interval (min) | N_Replen<br># replenish-ment intervals per hour (intervals/hr) | SE<br>Fraction Saliva Extraction | Freq_HtM<br>Number of hand-to-mouth contacts events per hour (events/hr) | Incidental oral Absorbed Dose (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assume Liquid Formulation -- Use of Davis Study (2008) and Liquid TCs** | | | | | | | | | | | | | |
| Cat (2596-49) | small | 1650 | 0.04 | 6.1 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0056 |
| | medium | 1650 | 0.04 | 3.7 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0033 |
| | large | 1650 | 0.04 | 2.3 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Dog (2596-50,62) | small | 2774 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0047 |
| | large | 4672 | 0.04 | 2.4 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Cat (2596-83) | small | 1752 | 0.04 | 6.5 | 150 | 0.0009 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0059 |
| | large | 3650 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0046 |
| Cat (2596-139) | small | 1460 | 0.04 | 5.4 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0049 |
| | medium | 1460 | 0.04 | 3.2 | 150 | 0.0004 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0030 |
| | large | 1460 | 0.04 | 2.0 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0018 |
| Dog (11556-164) | small | 3288 | 0.04 | 6.1 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0055 |
| | medium | 3288 | 0.04 | 2.6 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0024 |
| | large | 3288 | 0.04 | 1.7 | 150 | 0.0002 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0015 |
| Cat (11556-165) | small | 2055 | 0.04 | 7.6 | 150 | 0.0010 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0069 |
| | medium | 2055 | 0.04 | 4.6 | 150 | 0.0006 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0042 |
| | large | 2055 | 0.04 | 2.9 | 150 | 0.0004 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0026 |
| Dog (2596-84) | small | 2774 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0047 |
| | large | 4672 | 0.04 | 2.4 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Dog (2596-139) | small | 7300 | 0.04 | 13.5 | 150 | 0.0018 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0123 |
| | medium | 7300 | 0.04 | 5.8 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0053 |
| | large | 7300 | 0.04 | 3.7 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0034 |
| Cat (2596-63) | small | 2190 | 0.04 | 8.1 | 150 | 0.0011 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0074 |
| | large | 2482 | 0.04 | 3.5 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0031 |
| **Assume Dust Formulation -- Use of Davis Study (2008) and Dust TCs** | | | | | | | | | | | | | |
| Cat (2596-49) | small | 1650 | 0.37 | 166 | 150 | 0.2049 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.40 |
| | medium | 1650 | 0.37 | 100 | 150 | 0.1229 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.84 |
| | large | 1650 | 0.37 | 62 | 150 | 0.0768 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.52 |
| Dog (2596-50,62) | small | 2774 | 0.37 | 140 | 150 | 0.1723 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.18 |
| | large | 4672 | 0.37 | 64 | 150 | 0.0791 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.54 |
| Cat (2596-83) | small | 1752 | 0.37 | 176 | 150 | 0.2176 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.48 |

**Table I.1. Residential Post-application Non-cancer Incidental Oral Dose Assuming a Liquid or Dust Formulation for Pet Collars.**

| Animal Type | Animal Size | Application Rate (mg ai) | $F_{aihands}$ | DE Dermal Exposure (mg) | $SA_H$ Surface area of 1 hand ($cm^2$) | HR Hand residue loading ($mg/cm^2$) | $F_m$ Fraction of hand mouthed | ET Exposure Time (hours/day) | Replenish-ment interval (min) | N_Replen # replenish-ment intervals per hour (intervals/hr) | SE Fraction Saliva Extraction | Freq_HtM Number of hand-to-mouth contacts events per hour (events/hr) | Incidental oral Absorbed Dose (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | large | 3650 | 0.37 | 138 | 150 | 0.1700 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.16 |
| Cat (2596-139) | small | 1460 | 0.37 | 147 | 150 | 0.1813 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.24 |
| | medium | 1460 | 0.37 | 88 | 150 | 0.1088 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.74 |
| | large | 1460 | 0.37 | 55 | 150 | 0.0680 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.46 |
| Dog (11556-164) | small | 3288 | 0.37 | 166 | 150 | 0.2042 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.39 |
| | medium | 3288 | 0.37 | 71 | 150 | 0.0875 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.60 |
| | large | 3288 | 0.37 | 45 | 150 | 0.0557 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.38 |
| Cat (11556-165) | small | 2055 | 0.37 | 207 | 150 | 0.2552 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.74 |
| | medium | 2055 | 0.37 | 124 | 150 | 0.1531 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.04 |
| | large | 2055 | 0.37 | 78 | 150 | 0.0957 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.65 |
| Dog (2596-84) | small | 2774 | 0.37 | 140 | 150 | 0.1723 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.18 |
| | large | 4672 | 0.37 | 64 | 150 | 0.0791 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.54 |
| Dog (2596-139) | small | 7300 | 0.37 | 368 | 150 | 0.4533 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 3.09 |
| | medium | 7300 | 0.37 | 158 | 150 | 0.1943 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.33 |
| | large | 7300 | 0.37 | 100 | 150 | 0.1236 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.84 |
| Cat (2596-63) | small | 2190 | 0.37 | 221 | 150 | 0.2720 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.86 |
| | large | 2482 | 0.37 | 94 | 150 | 0.1156 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.79 |

1. Application rates are label defined. Refer to D426984.
2. Dermal Exposure (mg/day) = [Transfer Coefficient ($cm^2$/hr)] * [Application Rate (label defined) * Fraction Application Rate (0.0040; Davis, M. Et. al) ÷ Surface Area of Cat/Dog (Cat: Small, 1,500; Medium, 2,500; Large, 4,000 $cm^2$ - Dog: Small, 3,000; Medium, 7,000; Large, 11,000 $cm^2$)] x [Exposure Time (Adults, 0.77 hours/day; Children, 1.0 hours/day))
3. Incidental Oral Dose (mg/kg/day) = [Hand Residue Loading ($mg/cm^2$)] × [Fraction of Hand Mouthed (0.13) × Surface Area of 1 Child Hand (150 $cm^2$ )] x [Exposure Time (1.0 hrs/day) × # of Replenishment Intervals/hr (4 int/hr)) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (20 events/hr) ) ÷ ( # of Replenishment Intervals/hr))] / [Body Weight (11 kg child 1 to < 2 years old years old)]
   Where the Hand Residue Loading ($mg/cm^2$) = [$Fai_{hands}$ (Solid, 0.37; Liquids; 0.040) x Dermal Exposure (mg/day)] ÷ [Surface Area of 1 Child Hand (150 $cm^2$) x 2]

| Table I.2. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 1/99 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 1/99 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **2** |
| | | | Medium | 0.00334 | 0.83861 | **3.4** |
| | | | Large | 0.00209 | 0.52413 | **5.4** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **2.4** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **5.2** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **1.9** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **2.4** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **2.3** |
| | | | Medium | 0.00296 | 0.74213 | **3.8** |
| | | | Large | 0.00185 | 0.46383 | **6.1** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **2** |
| | | | Medium | 0.00238 | 0.59690 | **4.7** |
| | | | Large | 0.00151 | 0.37985 | **7.4** |
| 11556-165: Cat | Children 1 < 2 | 2,060 | Small | 0.00693 | 1.74096 | **1.6** |
| | | | Medium | 0.00416 | 1.04458 | **2.7** |
| | | | Large | 0.00260 | 0.65286 | **4.3** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **2.4** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **5.2** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **0.91** |
| | | | Medium | 0.00528 | 1.32524 | **2.1** |
| | | | Large | 0.00336 | 0.84333 | **3.4** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **1.5** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **3.6** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.01) + (Dust HtM Dose * 0.99)]. Bolded MOEs indicate a risk of concern.

| Table I.3. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 50/50 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 50/50 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **4** |
| | | | Medium | 0.00334 | 0.83861 | **6.7** |
| | | | Large | 0.00209 | 0.52413 | **11** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **4.7** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **10** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **3.8** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **4.8** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **4.5** |
| | | | Medium | 0.00296 | 0.74213 | **7.5** |
| | | | Large | 0.00185 | 0.46383 | **12** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **4** |
| | | | Medium | 0.00238 | 0.59690 | **9.3** |
| | | | Large | 0.00151 | 0.37985 | **15** |
| 11556-165: Cat | Children | 2,060 | Small | 0.00693 | 1.74096 | **3.2** |

| Table I.3. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 50/50 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 50/50 Liquid/Dust Combined MOE[4] |
| | 1 < 2 | | Medium | 0.00416 | 1.04458 | **5.3** |
| | | | Large | 0.00260 | 0.65286 | **8.5** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **4.7** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **10** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **1.8** |
| | | | Medium | 0.00528 | 1.32524 | **4.2** |
| | | | Large | 0.00336 | 0.84333 | **6.6** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **3** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **7.1** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.5) + (Dust HtM Dose * 0.5)]. Bolded MOEs indicate a risk of concern.

| Table I.4. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 99/1 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 99/1 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **140** |
| | | | Medium | 0.00334 | 0.83861 | **240** |
| | | | Large | 0.00209 | 0.52413 | **380** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **170** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **370** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **140** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **170** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **160** |
| | | | Medium | 0.00296 | 0.74213 | **270** |
| | | | Large | 0.00185 | 0.46383 | **430** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **140** |
| | | | Medium | 0.00238 | 0.59690 | **340** |
| | | | Large | 0.00151 | 0.37985 | **530** |
| 11556-165: Cat | Children 1 < 2 | 2,060 | Small | 0.00693 | 1.74096 | **120** |
| | | | Medium | 0.00416 | 1.04458 | **190** |
| | | | Large | 0.00260 | 0.65286 | **310** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **170** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **370** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **65** |
| | | | Medium | 0.00528 | 1.32524 | **150** |
| | | | Large | 0.00336 | 0.84333 | **240** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **110** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **250** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.99) + (Dust HtM Dose * 0.01)]. Bolded MOEs indicate a risk of concern.

| Table I.5. Residential Post-Application Non-Cancer Exposure and Risk Estimates from TCVP Dust/Powder and Pump/Trigger Spray Formulations. Incidental Oral LOC is an MOE = 1,000 | | | | | | |
|---|---|---|---|---|---|---|
| **EPA Reg. No./ Animal** | **Lifestage** | **Application Rate (mg ai)[1]** | **Animal Size** | **Dermal Exposure (mg/day)[2]** | **Incidental Oral Dose (mg/kg/day)[3]** | **MOE[4]** |
| **Dusts/Powders** | | | | | | |
| 47000-123: Dog | Children 1 < 2 | 170 | Small | 1.0 | 0.0087 | **320** |
| | | 430 | Medium | 1.1 | 0.0093 | **300** |
| | | 680 | Large | 1.1 | 0.0095 | **300** |
| 47000-123: Cat | Children 1 < 2 | 43 | Small | 0.52 | 0.0043 | **640** |
| | | 100 | Medium | 0.74 | 0.0063 | **450** |
| | | 150 | Large | 0.70 | 0.0059 | **480** |
| 2596-78: Cat | Children 1 < 2 | 280 | Small | 3.4 | 0.0287 | **98** |
| | | 470 | Large | 2.1 | 0.0180 | **160** |
| 2596-79: Dog | Children 1 < 2 | 470 | Small | 2.9 | 0.0240 | **120** |
| | | 940 | Medium | 2.4 | 0.0205 | **140** |
| | | 1,200 | Large | 1.9 | 0.0163 | **170** |
| 67517-82: Dog | Children 1 < 2 | 510 | Small | 3.1 | 0.0261 | **110** |
| | | 1,300 | Medium | 3.3 | 0.0280 | **100** |
| | | 2,000 | Large | 3.4 | 0.0285 | **98** |
| 67517-82: Cat | Children 1 < 2 | 130 | Small | 1.6 | 0.0130 | **210** |
| | | 310 | Medium | 2.2 | 0.0188 | **150** |
| | | 460 | Large | 2.1 | 0.0176 | **160** |
| **Pump/Trigger Sprays** | | | | | | |
| 2596-126, 140: Cat (Trigger) | Children 1 < 2 | 250 | Small | 1.9 | 0.00172 | 1,600 |
| | | 350 | Large | 0.99 | 0.00090 | 3,100 |
| 2596-140: Cat (Pump) | Children 1 < 2 | 51 | Small | 0.39 | 0.00035 | 8,000 |
| | | 71 | Large | 0.20 | 0.00018 | 15,000 |
| 2596-125, -140: Dog (Trigger) | Children 1 < 2 | 350 | Small | 1.3 | 0.00120 | 2,300 |
| | | 400 | Medium | 0.65 | 0.00059 | 4,800 |
| | | 700 | Large | 0.72 | 0.00066 | 4,300 |

1. Application rates are label defined. Refer to D426984.
2. Dermal Exposure (mg/day) = [Transfer Coefficient ($cm^2$/hr)] * [Application Rate (label defined) * Fraction Application Rate (Dust, 0.00048; Spray, 0.0081) ÷ Surface Area of Cat/Dog (Cat: Small, 1,500; Medium, 2,500; Large, 4,000 $cm^2$ - Dog: Small, 3,000; Medium, 7,000; Large, 11,000 $cm^2$)] x [Exposure Time (Adults, 0.77 hours/day; Children, 1.0 hours/day))]
3. Incidental Oral Dose (mg/kg/day) = [Hand Residue Loading (mg/$cm^2$)] × [Fraction of Hand Mouthed (0.13) × Surface Area of 1 Child Hand (150 $cm^2$ )] x [Exposure Time (1.0 hrs/day) × # of Replenishment Intervals/hr (4 int/hr)) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (20 events/hr) ) ÷ ( # of Replenishment Intervals/hr))] / [Body Weight (11 kg child 1 to < 2 years old years old)]
   Where the Hand Residue Loading (mg/$cm^2$) = [$Fai_{hands}$ (Dusts, 0.37; Liquids; 0.040) x Dermal Exposure (mg/day)] ÷ [Surface Area of 1 Child Hand (150 $cm^2$) x 2]
4. MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ Incidental Oral Dose (mg/kg/day). Bolded MOEs indicate a risk of concern.

## Appendix J. Summary of Residential Post-Application Cancer Exposure and Risks

| Table J.1. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar – 1/99 Ratio of Liquid/Dust Formulation | | | | | | |
|---|---|---|---|---|---|---|
| **Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **Combined 1/99 Liquid/Dust LADD[3]** | **Cancer Risk Estimate[4]** |
| **Exposure Data Source: Davis, M., et al (2008)** | | | | | | |
| 2596-49: Cat | Small | Adult | 5.8E-03 | 1.6E-01 | 1.5E-01 | 2.8E-04 |
| | Medium | | 3.5E-03 | 9.4E-02 | 9.3E-02 | 1.7E-04 |
| | Large | | 2.2E-03 | 5.8E-02 | 5.8E-02 | 1.1E-04 |
| 2596-50,62: Dog | Small | | 4.9E-03 | 1.3E-01 | 1.3E-01 | 2.4E-04 |
| | Large | | 2.2E-03 | 6.0E-02 | 6.0E-02 | 1.1E-04 |
| 2596-83: Cat | Small | | 6.2E-03 | 1.7E-01 | 1.6E-01 | 3.0E-04 |
| | Large | | 4.8E-03 | 1.3E-01 | 1.3E-01 | 2.3E-04 |
| 2596-139: Cat | Small | | 5.1E-03 | 1.4E-01 | 1.4E-01 | 2.5E-04 |
| | Medium | | 3.1E-03 | 8.3E-02 | 8.2E-02 | 1.5E-04 |
| | Large | | 1.9E-03 | 5.2E-02 | 5.1E-02 | 9.4E-05 |
| 11556-164: Dog | Small | | 5.8E-03 | 1.6E-01 | 1.5E-01 | 2.8E-04 |
| | Medium | | 2.5E-03 | 6.7E-02 | 6.6E-02 | 1.2E-04 |
| | Large | | 1.6E-03 | 4.2E-02 | 4.2E-02 | 7.7E-05 |
| 11556-165: Cat | Small | | 7.2E-03 | 1.9E-01 | 1.9E-01 | 3.5E-04 |
| | Medium | | 4.3E-03 | 1.2E-01 | 1.2E-01 | 2.1E-04 |
| | Large | | 2.7E-03 | 7.3E-02 | 7.2E-02 | 1.3E-04 |
| 2596-84: Dog | Small | | 4.9E-03 | 1.3E-01 | 1.3E-01 | 2.4E-04 |
| | Large | | 2.2E-03 | 6.0E-02 | 6.0E-02 | 1.1E-04 |
| 2596-139: Dog | Small | | 1.3E-02 | 3.5E-01 | 3.4E-01 | 6.3E-04 |
| | Medium | | 5.5E-03 | 1.5E-01 | 1.5E-01 | 2.7E-04 |
| | Large | | 3.5E-03 | 9.4E-02 | 9.3E-02 | 1.7E-04 |
| 2596-63: Cat | Small | | 7.7E-03 | 2.1E-01 | 2.1E-01 | 3.8E-04 |
| | Large | | 3.3E-03 | 8.8E-02 | 8.7E-02 | 1.6E-04 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 1/99 Liquid/Dust LADD = (Liquid LADD * 0.01) + (Dust LADD * 0.99)

4 Cancer risk estimates = Combined 1/99 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table J.2. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar - 50/50 Ratio of Liquid and Solid Formulation**

| Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | Combined 50/50 Liquid/Dust LADD[3] | Cancer Risk Estimate[4] |
|---|---|---|---|---|---|---|
| 2596-49: Cat | Small | Adult | 2.9E-03 | 7.8E-02 | 8.1E-02 | 1.5E-04 |
| | Medium | | 1.7E-03 | 4.7E-02 | 4.9E-02 | 8.9E-05 |
| | Large | | 1.1E-03 | 2.9E-02 | 3.0E-02 | 5.5E-05 |
| 2596-50,62: Dog | Small | | 2.4E-03 | 6.6E-02 | 6.8E-02 | 1.2E-04 |
| | Large | | 1.1E-03 | 3.0E-02 | 3.1E-02 | 5.7E-05 |
| 2596-83: Cat | Small | | 3.1E-03 | 8.3E-02 | 8.6E-02 | 1.6E-04 |
| | Large | | 2.4E-03 | 6.5E-02 | 6.7E-02 | 1.2E-04 |
| 2596-139: Cat | Small | | 2.6E-03 | 6.9E-02 | 7.2E-02 | 1.3E-04 |
| | Medium | | 1.5E-03 | 4.1E-02 | 4.3E-02 | 7.9E-05 |
| | Large | | 9.6E-04 | 2.6E-02 | 2.7E-02 | 4.9E-05 |
| 11556-164: Dog | Small | | 2.9E-03 | 7.8E-02 | 8.1E-02 | 1.5E-04 |
| | Medium | | 1.2E-03 | 3.3E-02 | 3.5E-02 | 6.3E-05 |
| | Large | | 7.9E-04 | 2.1E-02 | 2.2E-02 | 4.0E-05 |
| 11556-165: Cat | Small | | 3.6E-03 | 9.7E-02 | 1.0E-01 | 1.8E-04 |
| | Medium | | 2.2E-03 | 5.8E-02 | 6.0E-02 | 1.1E-04 |
| | Large | | 1.4E-03 | 3.6E-02 | 3.8E-02 | 6.9E-05 |
| 2596-84: Dog | Small | | 2.4E-03 | 6.6E-02 | 6.8E-02 | 1.2E-04 |
| | Large | | 1.1E-03 | 3.0E-02 | 3.1E-02 | 5.7E-05 |
| 2596-139: Dog | Small | | 6.4E-03 | 1.7E-01 | 1.8E-01 | 3.3E-04 |
| | Medium | | 2.7E-03 | 7.4E-02 | 7.7E-02 | 1.4E-04 |
| | Large | | 1.7E-03 | 4.7E-02 | 4.9E-02 | 8.9E-05 |
| 2596-63: Cat | Small | | 3.8E-03 | 1.0E-01 | 1.1E-01 | 2.0E-04 |
| | Large | | 1.6E-03 | 4.4E-02 | 4.6E-02 | 8.3E-05 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 50/50 Liquid/Dust LADD = (Liquid LADD * 0.5) + (Dust LADD * 0.5)

4 Cancer risk estimates = Combined 50/50 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ (mg/kg/day)$^{-1}$

**Table J.3. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar - 99/1 Ratio of Liquid and Solid Formulation**

| Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | Combined 99/1 Liquid/Dust LADD[3] | Cancer Risk Estimate[4] |
|---|---|---|---|---|---|---|
| 2596-49: Cat | Small | Adult | 5.7E-03 | 1.6E-03 | 7.3E-03 | 1.3E-05 |
| | Medium | | 3.4E-03 | 9.4E-04 | 4.4E-03 | 8.0E-06 |
| | Large | | 2.2E-03 | 5.8E-04 | 2.7E-03 | 5.0E-06 |
| 2596-50,62: Dog | Small | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| | Large | | 2.2E-03 | 6.0E-04 | 2.8E-03 | 5.2E-06 |
| 2596-83: Cat | Small | | 6.1E-03 | 1.7E-03 | 7.7E-03 | 1.4E-05 |
| | Large | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| 2596-139: Cat | Small | | 5.1E-03 | 1.4E-03 | 6.5E-03 | 1.2E-05 |
| | Medium | | 3.0E-03 | 8.3E-04 | 3.9E-03 | 7.1E-06 |
| | Large | | 1.9E-03 | 5.2E-04 | 2.4E-03 | 4.4E-06 |
| 11556-164: Dog | Small | | 5.7E-03 | 1.6E-03 | 7.3E-03 | 1.3E-05 |
| | Medium | | 2.4E-03 | 6.7E-04 | 3.1E-03 | 5.7E-06 |
| | Large | | 1.6E-03 | 4.2E-04 | 2.0E-03 | 3.6E-06 |
| 11556-165: Cat | Small | | 7.1E-03 | 1.9E-03 | 9.1E-03 | 1.7E-05 |
| | Medium | | 4.3E-03 | 1.2E-03 | 5.5E-03 | 1.0E-05 |
| | Large | | 2.7E-03 | 7.3E-04 | 3.4E-03 | 6.2E-06 |
| 2596-84: Dog | Small | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| | Large | | 2.2E-03 | 6.0E-04 | 2.8E-03 | 5.2E-06 |
| 2596-139: Dog | Small | | 1.3E-02 | 3.5E-03 | 1.6E-02 | 3.0E-05 |
| | Medium | | 5.4E-03 | 1.5E-03 | 6.9E-03 | 1.3E-05 |
| | Large | | 3.5E-03 | 9.4E-04 | 4.4E-03 | 8.1E-06 |
| 2596-63: Cat | Small | | 7.6E-03 | 2.1E-03 | 9.7E-03 | 1.8E-05 |
| | Large | | 3.2E-03 | 8.8E-04 | 4.1E-03 | 7.5E-06 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 99/1 Liquid/Dust LADD = (Liquid LADD * 0.99) + (Dust LADD * 0.01)

4 Cancer risk estimates = Combined 99/1 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ (mg/kg/day)$^{-1}$

| Table J.4. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Animal Type** | **Animal Size** | **Lifestage** | **LADD[1,2]** | **Cancer Risk Estimate[3]** |
| **Dust/Powder** | | | | |
| 47000-123: Dog | Small | Adult | 5.9E-04 | 1.1E-06 |
| | Medium | | 6.3E-04 | 1.2E-06 |
| | Large | | 6.4E-04 | 1.2E-06 |
| 47000-123: Cat | Small | | 2.9E-04 | 5.4E-07 |
| | Medium | | 4.2E-04 | 7.8E-07 |
| | Large | | 4.0E-04 | 7.3E-07 |
| 2596-78: Cat | Small | | 1.9E-03 | 3.6E-06 |
| | Large | | 1.2E-03 | 2.2E-06 |
| 2596-79: Dog | Small | | 1.6E-03 | 3.0E-06 |
| | Medium | | 1.4E-03 | 2.5E-06 |
| | Large | | 1.1E-03 | 2.0E-06 |
| 67517-82: Dog | Small | | 1.8E-03 | 3.2E-06 |
| | Medium | | 1.9E-03 | 3.5E-06 |
| | Large | | 1.9E-03 | 3.5E-06 |
| 67517-82: Cat | Small | | 8.8E-04 | 1.6E-06 |
| | Medium | | 1.3E-03 | 2.3E-06 |
| | Large | | 1.2E-03 | 2.2E-06 |
| **Pump/Trigger Spray** | | | | |
| 2596-126, 140: Cat (Trigger) | Small | Adult | 5.3E-04 | 9.6E-07 |
| | Large | | 2.8E-04 | 5.1E-07 |
| 2596-140: Cat (Pump) | Small | | 1.1E-04 | 2.0E-07 |
| | Large | | 5.6E-05 | 1.0E-07 |
| 2596-125, -140: Dog (Trigger) | Small | | 3.7E-04 | 6.7E-07 |
| | Medium | | 1.8E-04 | 3.3E-07 |
| | Large | | 2.0E-04 | 3.7E-07 |

1 Total Lifetime Average Daily Dose (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
2 Dermal and Inhalation LADD equations provided in Appendix B.
3 Cancer risk estimates = Total LADD × Q1*, where Q1* = $1.83 \times 10^{-3}$ (mg/kg/day)$^{-1}$

## Appendix K. Summary of Occupational Handler Non-Cancer Exposures and Risks



ED_002155B_00027906-00146

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Floors) | 0.00077 lb ai/sq ft | 100,000 (sq ft/day) | 2.5E-04 | 4.9E-05 | 2.5E-05 | 9.3E-05 | 16,000 | 81,000 | 160,000 | 43,000 |
| | Poultry Buildings (Floor Management, Fowl Tick) | 0.00064 lb ai/sq ft | | 2.0E-04 | 4.1E-05 | 2.0E-05 | 7.7E-05 | 19,000 | 97,000 | 190,000 | 51,000 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 4.1E-05 | 8.3E-06 | 4.1E-06 | 1.6E-05 | 95,000 | 480,000 | 950,000 | 250,000 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 2.0E-05 | 4.1E-06 | 2.0E-06 | 7.7E-06 | 190,000 | 970,000 | 1,900,000 | 510,000 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 4.9E-07 | 9.8E-08 | 4.9E-08 | 1.9E-07 | 8.1E+06 | 4.0E+07 | 8.1E+07 | 2.1E+07 |
| | | 0.064 lb ai/gallon | | 4.1E-07 | 8.1E-08 | 4.1E-08 | 1.5E-07 | 9.7E+06 | 4.8E+07 | 9.7E+07 | 2.6E+07 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick) | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.050 | 0.010 | 0.0050 | 0.00028 | **79** | 400 | 790 | 14,000 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 0.020 | 0.040 | 0.0020 | 0.00011 | **200** | 990 | 2,000 | 35,000 |
| (2b) Mixing/ Loading Wettable Powders for Paint Applications | Poultry (Floor Management – Roost) | 0.080 lb ai/gallon | 2 gallons | 1.0E-04 | 2.0E-05 | 1.0E-05 | 5.6E-07 | 40,000 | 200,000 | 400,000 | 7,100,000 |
| (3a) Mixing/ Loading Dusts for | | 0.030 lb ai/gallon | | 3.7E-05 | 7.5E-06 | 3.7E-06 | 2.1E-07 | 110,000 | 530,000 | 1,100,000 | 1.9E+07 |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Paint Applications (WP Data as Surrogate) | | | | | | | | | | | |
| **Applicators** | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 3.9E-04 | 7.9E-05 | 3.9E-05 | 5.0E-05 | 10,000 | 50,000 | 100,000 | 79,000 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 3.8E-04 | 7.6E-05 | 3.8E-05 | 4.8E-05 | 10,000 | 52,000 | 100,000 | 82,000 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3.2E-04 | 6.3E-05 | 3.2E-05 | 4.0E-05 | 12,000 | 63,000 | 120,000 | 99,000 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 1.6E-04 | 3.2E-05 | 1.6E-05 | 2.0E-05 | 25,000 | 120,000 | 250,000 | 200,000 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 6.4E-05 | 1.3E-05 | 6.4E-06 | 8.1E-06 | 61,000 | 310,000 | 610,000 | 490,000 |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 3.2E-05 | 6.3E-06 | 3.2E-06 | 4.0E-06 | 120,000 | 630,000 | 1,200,000 | 990,000 |
| (5) Open Pour Liquid Additive for | Cattle Feed (Concentrate) | 0.0039 lb ai/animal | 1,000 cows | 1.2E-05 | 2.5E-06 | 1.2E-06 | No Data | 320,000 | 1,600,000 | 3,200,000 | No Data |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 7.0E-06 | 1.4E-06 | 7.0E-07 | No Data | 560,000 | 2,800,000 | 5,600,000 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Feed Through Applications | Horse Feed | 0.0017 lb ai/animal | 500 horses | 2.7E-06 | 5.4E-07 | 2.7E-07 | No Data | 1,500,000 | 7,300,000 | 15,000,000 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 1.2E-05 | 2.4E-06 | 1.2E-06 | No Data | 330,000 | 1,700,000 | 3,300,000 | No Data |
| (6a) RTU Pet Collars - 1/99 liquid/dust ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 0.0072 | 0.0014 | 0.00072 | No Data | 550 | 2,700 | 5,500 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.012 | 0.0025 | 0.0012 | No Data | 320 | 1,600 | 3,200 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.020 | 0.0040 | 0.0020 | No Data | **200** | 980 | 2,000 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.0096 | 0.0019 | 0.00096 | No Data | 410 | 2,100 | 4,100 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.011 | 0.0022 | 0.0011 | No Data | 360 | 1,800 | 3,600 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.0078 | 0.0016 | 0.00078 | No Data | 500 | 2,500 | 5,000 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.016 | 0.0032 | 0.0016 | No Data | **250** | 1,200 | 2,500 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.012 | 0.0025 | 0.0012 | No Data | 320 | 1,600 | 3,200 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.020 | 0.0040 | 0.0020 | No Data | **200** | 980 | 2,000 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.0064 | 0.0013 | 0.00064 | No Data | 610 | 3,100 | 6,100 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.032 | 0.0064 | 0.0032 | No Data | **120** | 610 | 1,200 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.014 | 0.0029 | 0.0014 | No Data | **270** | 1,400 | 2,700 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.0090 | 0.0018 | 0.00090 | No Data | 440 | 2,200 | 4,400 | No Data |
| (6b) RTU Pet Collars - 50/50 | Cat (2596-49) | 0.0036 lb ai/animal | | 0.0037 | 0.00073 | 0.00037 | No Data | 1,100 | 5,400 | 11,000 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.0062 | 0.0012 | 0.00062 | No Data | 640 | 3,200 | 6,400 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| liquid/dust ratio | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.010 | 0.0020 | 0.0010 | No Data | 390 | 1,900 | 3,900 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.0049 | 0.00097 | 0.00049 | No Data | 810 | 4,100 | 8,100 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 700 | 3,500 | 7,000 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.0040 | 0.00079 | 0.00040 | No Data | 1,000 | 5,000 | 10,000 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.0081 | 0.0016 | 0.00081 | No Data | 490 | 2,400 | 4,900 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.0062 | 0.0012 | 0.00062 | No Data | 640 | 3,200 | 6,400 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.010 | 0.0020 | 0.0010 | No Data | 390 | 1,900 | 3,900 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.0032 | 0.00065 | 0.00032 | No Data | 1,200 | 6,100 | 12,000 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.016 | 0.0032 | 0.0016 | No Data | **240** | 1,200 | 2,400 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.0073 | 0.001465 | 0.00073 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.0046 | 0.00092 | 0.00046 | No Data | 860 | 4,300 | 8,600 | No Data |
| (6c) RTU Pet Collars - 99/1 liquid/dust ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 0.000073 | 0.000015 | 0.0000073 | No Data | 54,000 | 270,000 | 540,000 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.00012 | 0.000025 | 0.000012 | No Data | 32,000 | 160,000 | 320,000 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.00020 | 0.000041 | 0.000020 | No Data | 19,000 | 97,000 | 190,000 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.000097 | 0.000019 | 0.000010 | No Data | 40,000 | 200,000 | 400,000 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.00011 | 0.000022 | 0.000011 | No Data | 35,000 | 180,000 | 350,000 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.000079 | 0.000016 | 0.0000079 | No Data | 50,000 | 250,000 | 500,000 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Inhalation Dose (mg/kg/day) | | | | Inhalation MOEs (LOC is an MOE = 300) For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | No R | PF5 R | PF10 R | EC | No R | PF5 R | PF10 R | EC |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.00016 | 0.000033 | 0.000016 | No Data | 24,000 | 120,000 | 240,000 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.00012 | 0.000025 | 0.000012 | No Data | 32,000 | 160,000 | 320,000 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.00020 | 0.000041 | 0.000020 | No Data | 19,000 | 97,000 | 190,000 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.000065 | 0.000013 | 0.0000065 | No Data | 61,000 | 300,000 | 610,000 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.00033 | 0.000065 | 0.000033 | No Data | 12,000 | 61,000 | 120,000 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.00015 | 0.000029 | 0.000015 | No Data | 27,000 | 130,000 | 270,000 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.000091 | 0.000018 | 0.0000091 | No Data | 43,000 | 220,000 | 430,000 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 0.00075 | 0.00015 | 0.000075 | No Data | 5,200 | 26,000 | 52,000 | 5,200 |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 0.0019 | 0.00038 | 0.00019 | No Data | 2,100 | 10,000 | 21,000 | 2,100 |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 0.0030 | 0.00061 | 0.00030 | No Data | 1,300 | 6,500 | 13,000 | 1,300 |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 0.00018 | 0.000037 | 0.000018 | No Data | 22,000 | 110,000 | 220,000 | 22,000 |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 0.00045 | 0.000089 | 0.000045 | No Data | 8,800 | 44,000 | 88,000 | 8,800 |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 0.00069 | 0.00014 | 0.000069 | No Data | 5,700 | 29,000 | 57,000 | 5,700 |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 0.0013 | 0.00025 | 0.00013 | No Data | 3,100 | 16,000 | 31,000 | 3,100 |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | 1,900 |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | No Data |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 0.0043 | 0.00085 | 0.00043 | No Data | 920 | 4,600 | 9,200 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 0.0053 | 0.0011 | 0.00053 | No Data | 750 | 3,700 | 7,500 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 0.0022 | 0.00045 | 0.00022 | No Data | 1,800 | 8,800 | 18,000 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 0.0057 | 0.0011 | 0.00057 | No Data | 690 | 3,500 | 6,900 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 0.0091 | 0.0018 | 0.00091 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 0.00057 | 0.00011 | 0.000057 | No Data | 6,900 | 35,000 | 69,000 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 0.0014 | 0.00027 | 0.00014 | No Data | 2,900 | 14,000 | 29,000 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 0.00021 | 0.000042 | 0.000021 | No Data | 19,000 | 94,000 | 190,000 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 0.00029 | 0.000059 | 0.000029 | No Data | 13,000 | 67,000 | 130,000 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 0.000042 | 0.0000084 | 0.0000042 | No Data | 94,000 | 470,000 | 940,000 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 0.000061 | 0.000012 | 0.0000061 | No Data | 64,000 | 320,000 | 640,000 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 0.00029 | 0.000059 | 0.000029 | No Data | 13,000 | 67,000 | 130,000 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 0.00034 | 0.000067 | 0.000034 | No Data | 12,000 | 58,000 | 120,000 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 0.00057 | 0.00012 | 0.000057 | No Data | 6,900 | 34,000 | 69,000 | No Data |
| **Mixers/Loaders/Applicators** | | | | | | | | | | | |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.0068 | 0.0014 | 0.00068 | No Data | 580 | 2,900 | 5,800 | No Data |
| | | 0.032 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Woody Borders of Kennels, Yards, | 0.032 lb ai/sq ft | 1,000 sq ft | 0.014 | 0.0028 | 0.0014 | No Data | **280** | 1,400 | 2,800 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Campgrounds, Recreational Parks, Footpaths and Roadways | | (spot) | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 0.0045 | 0.00090 | 0.00045 | No Data | 870 | 4,400 | 8,700 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 0.0085 | 0.0017 | 0.00085 | No Data | 460 | 2,300 | 4,600 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 0.00085 | 0.00017 | 0.000085 | No Data | 4,600 | 23,000 | 46,000 | No Data |
| | | 0.0013 lb ai/animal | | 0.00023 | 0.000045 | 0.000023 | No Data | 17,000 | 87,000 | 170,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.0067 | 0.0013 | 0.00067 | No Data | 590 | 2,900 | 5,900 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0011 | 0.00023 | 0.00011 | No Data | 3,500 | 17,000 | 35,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.00068 | 0.00014 | 0.000068 | No Data | 5,800 | 29,000 | 58,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.00056 | 0.00011 | 0.000056 | No Data | 7,100 | 35,000 | 71,000 | No Data |
| (9b) Liquid: Manually-Pressurized Handwand | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.0068 | 0.0014 | 0.00068 | No Data | 580 | 2,900 | 5,800 | No Data |
| | | 0.032 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 0.0139 | 0.0028 | 0.0014 | No Data | **280** | 1,400 | 2,800 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Recreational Parks, Footpaths and Roadways | | | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 0.0045 | 0.00090 | 0.00045 | No Data | 870 | 4,400 | 8,700 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 0.0085 | 0.0017 | 0.00085 | No Data | 460 | 2,300 | 4,600 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 0.00085 | 0.00017 | 0.000085 | No Data | 4,600 | 23,000 | 46,000 | No Data |
| | | 0.0013 lb ai/animal | | 0.00023 | 0.00045 | 0.000023 | No Data | 17,000 | 87,000 | 170,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.0067 | 0.0013 | 0.00067 | No Data | 590 | 2,900 | 5,900 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0028 | 0.00054 | 0.00027 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0011 | 0.00023 | 0.00011 | No Data | 3,500 | 17,000 | 35,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.00068 | 0.00014 | 0.000068 | No Data | 5,800 | 29,000 | 58,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.00056 | 0.00011 | 0.000056 | No Data | 7,100 | 35,000 | 71,000 | No Data |
| (9c) Liquid: Mechanically -Pressurized Handgun | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.018 | 0.0036 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | | 0.032 lb ai/animal | | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, | 0.026 lb ai/animal | | 0.012 | 0.0024 | 0.0012 | No Data | 330 | 1,700 | 3,300 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Footpaths and Roadways | | | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 0.023 | 0.0045 | 0.0023 | No Data | **180** | 880 | 1,800 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 0.0023 | 0.00045 | 0.00023 | No Data | 1,800 | 8,800 | 18,000 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 0.00060 | 0.00012 | 0.000060 | No Data | 6,600 | 33,000 | 66,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.018 | 0.0035 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0073 | 0.0015 | 0.00073 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0030 | 0.00060 | 0.00023 | No Data | 1,300 | 6,600 | 13,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.0018 | 0.00036 | 0.00018 | No Data | 2,200 | 11,000 | 22,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.0015 | 0.00029 | 0.00015 | No Data | 2,700 | 13,000 | 27,000 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 (gallons/ day) | 1.2E-05 | 2.5E-06 | 1.2E-06 | No Data | 320,000 | 1,600,000 | 3,200,000 | No Data |
| | | 0.064 lb ai/gallon | | 1.0E-05 | 2.0E-06 | 1.0E-06 | No Data | 390,000 | 1,900,000 | 3,900,000 | No Data |
| (10a) Wettable Powder: Backpack Sprayer | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Poultry (Floor Management Litter, | 0.00080 lb ai/sq ft | 20,000 sq ft | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | | 0.0014 | 0.00028 | 0.00014 | No Data | 2,800 | 14,000 | 28,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 0.00070 | 0.00014 | 0.000070 | No Data | 5,700 | 28,000 | 57,000 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 0.000017 | 0.0000035 | 0.0000017 | No Data | 230,000 | 1,100,000 | 2,300,000 | No Data |
| (10b) Wettable Powder: Manually-Pressurized Handwand | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure | 0.00080 lb ai/sq ft | 20,000 sq ft | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0014 | 0.00028 | 0.00014 | No Data | 2,800 | 14,000 | 28,000 | No Data |
| | | 0.000080 lb ai/sq ft | | 0.00070 | 0.00014 | 0.000070 | No Data | 5,700 | 28,000 | 57,000 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 0.000017 | 0.0000035 | 0.0000017 | No Data | 230,000 | 1,100,000 | 2,300,000 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 4.13 | 0.828 | 0.413 | No Data | **1** | **5** | **10** | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 10.10 | 2.010 | 1.010 | No Data | **0** | **2** | **4** | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 2.97 | 0.594 | 0.297 | No Data | **1** | **7** | **13** | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - Plunger Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 0.11 | 0.023 | 0.011 | No Data | **35** | **180** | 350 | No Data |
| (10f) Wettable Powder: Plunger | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 0.039 | 0.0078 | 0.0039 | No Data | **100** | 500 | 1,000 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 0.019 | 0.0038 | 0.0019 | No Data | **210** | 1,000 | 2,100 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Duster (Dust Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 700 | 3,500 | 7,000 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 0.18 | 0.037 | 0.018 | No Data | **21** | **110** | **210** | No Data |
| | | 0.38 lb ai/dust bag | | 0.093 | 0.019 | 0.0093 | No Data | **42** | **210** | 420 | No Data |
| | | 0.13 lb ai/dust bag | | 0.032 | 0.0064 | 0.0032 | No Data | **120** | 620 | 1,200 | No Data |
| (11b) Dust: Shaker Can | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 0.76 | 0.15 | 0.076 | No Data | **5** | **26** | **52** | No Data |
| | | 0.0038 lb ai/animal | | 0.39 | 0.077 | 0.039 | No Data | **10** | **51** | **100** | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 0.13 | 0.026 | 0.013 | No Data | **30** | **150** | 300 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/ bird | 1,000 birds | 0.15 | 0.030 | 0.015 | No Data | **26** | **130** | **260** | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 0.076 | 0.015 | 0.0076 | No Data | **52** | **260** | 520 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 0.051 | 0.010 | 0.0051 | No Data | **78** | 390 | 780 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/ bird | 1,000 birds | 0.025 | 0.0051 | 0.0025 | No Data | **160** | 780 | 1,600 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 0.074 | 0.015 | 0.0074 | No Data | **54** | **270** | 540 | No Data |
| | | 0.0038 lb ai/animal | | 0.037 | 0.0075 | 0.0037 | No Data | **110** | 530 | 1,100 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 0.013 | 0.0026 | 0.0013 | No Data | 310 | 1,500 | 3,100 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 0.29 | 0.060 | 0.029 | No Data | **13** | **67** | **130** | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 0.15 | 0.029 | 0.015 | No Data | **27** | **130** | **270** | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 0.049 | 0.0098 | 0.0049 | No Data | **80** | 400 | 800 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/ sq ft | 1,000 sq ft | 0.0074 | 0.0015 | 0.00074 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 0.0025 | 0.00049 | 0.00025 | No Data | 1,600 | 8,000 | 16,000 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 0.00065 | 0.00013 | 0.000065 | No Data | 6,100 | 30,000 | 61,000 | No Data |
| | | 0.077 lb ai/gallon | | 0.00063 | 0.00013 | 0.000063 | No Data | 6,300 | 32,000 | 63,000 | No Data |
| | | 0.064 lb ai/gallon | | 0.00052 | 0.00010 | 0.000052 | No Data | 7,600 | 38,000 | 76,000 | No Data |
| | | 0.03 lb ai/gallon | | 0.00024 | 0.000049 | 0.000024 | No Data | 16,000 | 81,000 | 160,000 | No Data |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 0.0013 | 0.00026 | 0.00013 | No Data | 3,000 | 15,000 | 30,000 | No Data |
| | | 0.077 lb ai/gallon | | 0.0013 | 0.00025 | 0.00013 | No Data | 3,200 | 16,000 | 32,000 | No Data |
| | | 0.064 lb ai/gallon | | 0.0010 | 0.00021 | 0.00010 | No Data | 3,800 | 19,000 | 38,000 | No Data |
| | | 0.03 lb ai/gallon | | 0.00049 | 0.000097 | 0.000049 | No Data | 8,100 | 40,000 | 81,000 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 0.00014 | 0.000027 | 0.000014 | No Data | 29,000 | 140,000 | 290,000 | No Data |
| | | 0.00077 lb ai/animal | | 0.000070 | 0.000014 | 0.0000070 | No Data | 57,000 | 280,000 | 570,000 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 0.00040 | 0.000080 | 0.000040 | No Data | 9,900 | 49,000 | 99,000 | No Data |
| | | 0.0017 lb ai/animal | | 0.00031 | 0.000062 | 0.000031 | No Data | 13,000 | 64,000 | 130,000 | No Data |

| Table K.2. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | No Data | No Data | No Data | 570 | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/ sq ft | 100,000 sq ft | 0.035 | No Data | No Data | No Data | **110** | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.014 | No Data | No Data | No Data | **280** | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0070 | No Data | No Data | No Data | 570 | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0016 | No Data | No Data | No Data | 2,400 | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.00081 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.0081 | No Data | No Data | No Data | 490 | No Data | No Data | No Data |

| Table K.2. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.00081 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.0033 | No Data | No Data | No Data | 1,200 | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0016 | No Data | No Data | No Data | 2,400 | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | 0.000812 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| **Mixer/Loader/Applicators** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.018 | 0.0037 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.092 | 0.018 | 0.0092 | No Data | **43** | **220** | 430 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.037 | 0.0073 | 0.0037 | No Data | **110** | 540 | 1,100 | No Data |
| | | 0.00016 lb ai/sq ft | | 0.018 | 0.0037 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | | 0.000080 lb ai/sq ft | | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |

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## Appendix L. Summary of Occupational Handler Cancer Risk Estimates



ED_002155B_00027906-00163

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | 100,000 sq ft | 5E-07 | 9E-08 | 7E-08 | 5E-07 | 9E-08 | 7E-08 | 5E-07 | 9E-08 | 7E-08 | 2E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 4E-07 | 8E-08 | 6E-08 | 4E-07 | 8E-08 | 6E-08 | 4E-07 | 7E-08 | 6E-08 | 2E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 9E-08 | 2E-08 | 1E-08 | 9E-08 | 2E-08 | 1E-08 | 9E-08 | 2E-08 | 1E-08 | 4E-09 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 7E-09 | 6E-09 | 2E-09 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 1E-09 | 2E-10 | 1E-10 | 1E-09 | 2E-10 | 1E-10 | 1E-09 | 2E-10 | 1E-10 | 5E-11 |
| | | 0.064 lb ai/gallon | | 9E-10 | 2E-10 | 1E-10 | 9E-10 | 2E-10 | 1E-10 | 9E-10 | 1E-10 | 1E-10 | 4E-11 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 1E-05 | 2E-06 | 1E-06 | 9E-06 | 6E-07 | 5E-07 | 9E-06 | 5E-07 | 4E-07 | 3E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/ sq ft | | 4E-06 | 6E-07 | 6E-07 | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 2E-07 | 2E-07 | 1E-08 |
| (2b) Mixing/ Loading Wettable Powders for | Poultry (Floor Management – Roost) | 0.080 lb ai/gallon | 2 gallons | 8E-09 | 1E-09 | 1E-09 | 7E-09 | 5E-10 | 4E-10 | 7E-09 | 4E-10 | 3E-10 | 2E-11 |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Paint Applications | | | | | | | | | | | | | |
| (3a) Mixing/ Loading Dusts for Paint Applications (WP Data as Surrogate) | | 0.030 lb ai/gallon | | 8E-09 | 1E-09 | 1E-09 | 7E-09 | 5E-10 | 4E-10 | 7E-09 | 4E-10 | 3E-10 | 2E-11 |
| **Applicators** | | | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 4E-08 | 3E-08 | 1E-08 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 4E-08 | 3E-08 | 1E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 1E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 8E-08 | 2E-08 | 2E-08 | 8E-08 | 2E-08 | 1E-08 | 8E-08 | 2E-08 | 1E-08 | 5E-09 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 3E-08 | 8E-09 | 6E-09 | 3E-08 | 7E-09 | 5E-09 | 3E-08 | 7E-09 | 5E-09 | 2E-09 |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 3E-09 | 3E-09 | 1E-09 |
| | Cattle Feed | 0.0039 | 1,000 | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 3E-09 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (5) Open Pour Liquid Additive for Feed Through Applications | (Concentrate) | lb ai/animal | cows | | | | | | | | | | |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 2E-08 | 3E-09 | 2E-09 | 1E-08 | 3E-09 | 2E-09 | 1E-08 | 3E-09 | 2E-09 | No Data |
| | Horse Feed | 0.0017 lb ai/animal | 500 horses | 6E-09 | 1E-09 | 8E-10 | 6E-09 | 1E-09 | 8E-10 | 6E-09 | 1E-09 | 8E-10 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 4E-09 | 3E-09 | 3E-08 | 4E-09 | 3E-09 | No Data |
| (6a) RTU Pet Collar Applications – 1/99 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 1E-07 | 1E-07 | 4E-06 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 6E-06 | 4E-07 | 4E-07 | 6E-06 | 2E-07 | 2E-07 | 6E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 6E-06 | 4E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 1E-07 | 1E-07 | 4E-06 | 1E-07 | 9E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 8E-06 | 6E-07 | 5E-07 | 8E-06 | 3E-07 | 2E-07 | 8E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 6E-06 | 4E-07 | 4E-07 | 6E-06 | 2E-07 | 2E-07 | 6E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 9E-08 | 3E-06 | 1E-07 | 7E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 6E-07 | 4E-07 | 2E-05 | 5E-07 | 4E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 7E-06 | 5E-07 | 4E-07 | 7E-06 | 3E-07 | 2E-07 | 7E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 1E-07 | 1E-07 | No Data |
| (6b) RTU Pet Collar | Cat (2596-49) | 0.0036 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 1E-07 | 7E-08 | 2E-06 | 9E-08 | 6E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Applications – 50/50 Liquid/Dust Ratio | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 3E-06 | 3E-07 | 2E-07 | 3E-06 | 2E-07 | 1E-07 | 3E-06 | 1E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 2E-06 | 1E-07 | 9E-08 | 2E-06 | 1E-07 | 8E-08 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 1E-07 | 3E-06 | 1E-07 | 9E-08 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 1E-07 | 7E-08 | 2E-06 | 9E-08 | 6E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 4E-06 | 4E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 3E-06 | 3E-07 | 2E-07 | 3E-06 | 2E-07 | 1E-07 | 3E-06 | 1E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 2E-06 | 1E-07 | 1E-07 | 2E-06 | 8E-08 | 6E-08 | 2E-06 | 8E-08 | 5E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 9E-06 | 7E-07 | 6E-07 | 8E-06 | 4E-07 | 3E-07 | 8E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 4E-06 | 3E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 2E-06 | 2E-07 | 2E-07 | 2E-06 | 1E-07 | 8E-08 | 2E-06 | 1E-07 | 7E-08 | No Data |
| (6c) RTU Pet Collar Applications – 99/1 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 1E-07 | 6E-08 | 4E-08 | 1E-07 | 6E-08 | 4E-08 | 1E-07 | 6E-08 | 4E-08 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 2E-07 | 1E-07 | 7E-08 | 2E-07 | 1E-07 | 6E-08 | 2E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 6E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 1E-07 | 7E-08 | 4E-08 | 1E-07 | 7E-08 | 4E-08 | 1E-07 | 7E-08 | 4E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 3E-07 | 1E-07 | 9E-08 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 2E-07 | 1E-07 | 7E-08 | 2E-07 | 1E-07 | 6E-08 | 2E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 1E-07 | 6E-08 | 3E-08 | 1E-07 | 5E-08 | 3E-08 | 1E-07 | 5E-08 | 3E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 4E-07 | 3E-08 | 2E-08 | 4E-07 | 1E-08 | 1E-08 | 4E-07 | 1E-08 | 8E-09 | No Data |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 9E-07 | 3E-08 | 3E-08 | 9E-07 | 3E-08 | 2E-08 | No Data |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 2E-06 | 1E-07 | 9E-08 | 2E-06 | 5E-08 | 4E-08 | 2E-06 | 5E-08 | 3E-08 | No Data |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 9E-08 | 6E-09 | 6E-09 | 9E-08 | 3E-09 | 2E-09 | 9E-08 | 3E-09 | 2E-09 | No Data |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 2E-07 | 2E-08 | 1E-08 | 2E-07 | 8E-09 | 6E-09 | 2E-07 | 7E-09 | 5E-09 | No Data |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 4E-07 | 2E-08 | 2E-08 | 3E-07 | 1E-08 | 9E-09 | 3E-07 | 1E-08 | 8E-09 | No Data |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 6E-07 | 4E-08 | 4E-08 | 6E-07 | 2E-08 | 2E-08 | 6E-07 | 2E-08 | 1E-08 | No Data |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 8E-08 | 6E-08 | 2E-06 | 7E-08 | 5E-08 | No Data |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 9E-08 | 7E-08 | 3E-06 | 8E-08 | 6E-08 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 1E-06 | 8E-08 | 7E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 8E-08 | 3E-06 | 9E-08 | 6E-08 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 1E-07 | 1E-07 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 3E-07 | 2E-08 | 2E-08 | 3E-07 | 1E-08 | 8E-09 | 3E-07 | 9E-09 | 6E-09 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 7E-07 | 5E-08 | 4E-08 | 7E-07 | 2E-08 | 2E-08 | 7E-07 | 2E-08 | 2E-08 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 8E-08 | 7E-08 | 4E-08 | 7E-08 | 7E-08 | 4E-08 | 7E-08 | 7E-08 | 4E-08 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 5E-08 | 1E-07 | 1E-07 | 5E-08 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 2E-08 | 1E-08 | 8E-09 | 1E-08 | 1E-08 | 8E-09 | 1E-08 | 1E-08 | 7E-09 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 2E-08 | 2E-08 | 1E-08 | 2E-08 | 2E-08 | 1E-08 | 2E-08 | 2E-08 | 1E-08 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 5E-08 | 1E-07 | 1E-07 | 5E-08 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 1E-07 | 1E-07 | 7E-08 | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| Mixers/Loaders/Applicators | | | | | | | | | | | | | |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | | 0.032 lb ai/animal | | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 7E-07 | 1E-06 | 1E-06 | 6E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 2E-06 | 2E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 9E-07 | 9E-07 | 6E-07 | 8E-07 | 8E-07 | 5E-07 | 8E-07 | 8E-07 | 5E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| | | 0.0013 lb ai/animal | | 5E-08 | 5E-08 | 3E-08 | 4E-08 | 4E-08 | 3E-08 | 4E-08 | 4E-08 | 3E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 7E-07 | 1E-06 | 1E-06 | 6E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 6E-07 | 6E-07 | 4E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-07 | 2E-07 | 2E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 7E-08 | 1E-07 | 1E-07 | 6E-08 | No Data |
| (9b) Liquid: Manually-Pressurized Handwand | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | | 0.032 lb ai/animal | | 4E-05 | 3E-07 | 3E-07 | 4E-05 | 2E-07 | 2E-07 | 4E-05 | 2E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 1E-04 | 7E-07 | 7E-07 | 1E-04 | 5E-07 | 4E-07 | 1E-04 | 5E-07 | 4E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 3E-05 | 2E-07 | 2E-07 | 3E-05 | 2E-07 | 1E-07 | 3E-05 | 1E-07 | 1E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 6E-06 | 4E-08 | 4E-08 | 6E-06 | 3E-08 | 3E-08 | 6E-06 | 3E-08 | 2E-08 | No Data |
| | | 0.0013 lb ai/animal | | 2E-06 | 1E-08 | 1E-08 | 2E-06 | 8E-09 | 7E-09 | 2E-06 | 7E-09 | 6E-09 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 4E-05 | 3E-07 | 3E-07 | 4E-05 | 2E-07 | 2E-07 | 4E-05 | 2E-07 | 2E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 8E-08 | 2E-05 | 9E-08 | 8E-08 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 8E-06 | 6E-08 | 5E-08 | 8E-06 | 4E-08 | 3E-08 | 8E-06 | 4E-08 | 3E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 4E-06 | 3E-08 | 3E-08 | 4E-06 | 2E-08 | 2E-08 | 4E-06 | 2E-08 | 2E-08 | No Data |
| (9c) Liquid: Mechanically -Pressurized Handgun | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 1E-06 | 7E-07 | 6E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 3E-07 | 2E-07 | No Data |
| | | 0.032 lb ai/animal | | 1E-06 | 6E-07 | 5E-07 | 8E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.026 lb ai/animal | | 8E-07 | 5E-07 | 4E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 2E-07 | 1E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 2E-06 | 9E-07 | 7E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 4E-07 | 3E-07 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 2E-07 | 9E-08 | 7E-08 | 1E-07 | 5E-08 | 3E-08 | 1E-07 | 4E-08 | 3E-08 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 4E-08 | 2E-08 | 2E-08 | 3E-08 | 1E-08 | 8E-09 | 3E-08 | 1E-08 | 7E-09 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-06 | 7E-07 | 6E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 3E-07 | 2E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 6E-07 | 5E-07 | 8E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 5E-07 | 3E-07 | 2E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 1E-07 | 9E-08 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-07 | 1E-07 | 9E-08 | 2E-07 | 6E-08 | 4E-08 | 2E-07 | 6E-08 | 4E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-07 | 7E-08 | 6E-08 | 9E-08 | 4E-08 | 3E-08 | 9E-08 | 3E-08 | 2E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-07 | 6E-08 | 5E-08 | 8E-08 | 3E-08 | 2E-08 | 7E-08 | 3E-08 | 2E-08 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 (gallons/ day) | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 3E-09 | 3E-08 | 5E-09 | 3E-09 | No Data |
| | | 0.064 lb ai/gallon | | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 4E-09 | 3E-09 | No Data |
| (10a) Wettable | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Powder: Backpack Sprayer | Swine - Direct Spray | 0.020 lb ai/animal | | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/ sq ft | | 6E-07 | 6E-07 | 4E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | 20,000 sq ft | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 2E-07 | 2E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 3E-09 | 3E-09 | 2E-09 | 3E-09 | 3E-09 | 2E-09 | 3E-09 | 3E-09 | 2E-09 | No Data |
| (10b) Wettable Powder: Manually-Pressurized Handwand | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 1E-07 | No Data |
| | Poultry (Floor Management Litter, | 0.00080 lb ai/sq ft | 20,000 sq ft | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 1E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 8E-08 | 2E-05 | 9E-08 | 8E-08 | No Data |
| | | 0.00016 lb ai/sq ft | | 1E-05 | 7E-08 | 7E-08 | 1E-05 | 5E-08 | 4E-08 | 1E-05 | 5E-08 | 4E-08 | No Data |
| | | 0.000080 lb ai/sq ft | | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 1E-07 | 9E-10 | 8E-10 | 1E-07 | 6E-10 | 5E-10 | 1E-07 | 6E-10 | 5E-10 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 9E-05 | 9E-05 | 9E-05 | 2E-05 | 2E-05 | 2E-05 | 9E-06 | 9E-06 | 9E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 2E-04 | 2E-04 | 2E-04 | 4E-05 | 4E-05 | 4E-05 | 2E-05 | 2E-05 | 2E-05 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 7E-05 | 7E-05 | 7E-05 | 1E-05 | 1E-05 | 1E-05 | 7E-06 | 7E-06 | 7E-06 | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - Plunger Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| (10f) Wettable Powder: Plunger | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 9E-06 | 2E-06 | 2E-06 | 8E-06 | 1E-06 | 1E-06 | 8E-06 | 1E-06 | 1E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 4E-06 | 1E-06 | 9E-07 | 4E-06 | 7E-07 | 6E-07 | 4E-06 | 6E-07 | 5E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Duster (Dust Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 1E-06 | 3E-07 | 3E-07 | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 4E-05 | 1E-05 | 9E-06 | 4E-05 | 7E-06 | 6E-06 | 4E-05 | 6E-06 | 5E-06 | No Data |
| | | 0.38 lb ai/dust bag | | 2E-05 | 5E-06 | 4E-06 | 2E-05 | 3E-06 | 3E-06 | 2E-05 | 3E-06 | 3E-06 | No Data |
| | | 0.13 lb ai/dust bag | | 7E-06 | 2E-06 | 2E-06 | 7E-06 | 1E-06 | 1E-06 | 7E-06 | 1E-06 | 9E-07 | No Data |
| (11b) Dust: Shaker Can | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 4E-04 | 3E-05 | 2E-05 | 4E-04 | 1E-05 | 1E-05 | 4E-04 | 1E-05 | 8E-06 | No Data |
| | | 0.0038 lb ai/animal | | 2E-04 | 1E-05 | 1E-05 | 2E-04 | 7E-06 | 5E-06 | 2E-04 | 6E-06 | 4E-06 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 7E-05 | 5E-06 | 4E-06 | 7E-05 | 2E-06 | 2E-06 | 6E-05 | 2E-06 | 1E-06 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 8E-05 | 5E-06 | 5E-06 | 8E-05 | 3E-06 | 2E-06 | 8E-05 | 2E-06 | 2E-06 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 4E-05 | 3E-06 | 2E-06 | 4E-05 | 1E-06 | 1E-06 | 4E-05 | 1E-06 | 8E-07 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 9E-07 | 7E-07 | 3E-05 | 8E-07 | 6E-07 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 1E-05 | 9E-07 | 8E-07 | 1E-05 | 5E-07 | 3E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | | 0.0038 lb ai/animal | | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 1E-05 | 2E-06 | 1E-06 | 1E-05 | 2E-06 | 1E-06 | 1E-05 | 2E-06 | 1E-06 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 3E-04 | 4E-05 | 4E-05 | 3E-04 | 4E-05 | 3E-05 | 3E-04 | 4E-05 | 3E-05 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | No Data |
| | | 0.077 lb ai/gallon | | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | No Data |
| | | 0.064 lb ai/gallon | | 7E-08 | 1E-08 | 1E-08 | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | No Data |
| | | 0.03 lb ai/gallon | | 3E-07 | 5E-08 | 5E-08 | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 4E-08 | 4E-08 | No Data |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 2E-07 | 9E-08 | 8E-08 | 2E-07 | 6E-08 | 6E-08 | 2E-07 | 6E-08 | 6E-08 | No Data |
| | | 0.077 lb ai/gallon | | 2E-07 | 8E-08 | 8E-08 | 2E-07 | 6E-08 | 6E-08 | 2E-07 | 6E-08 | 5E-08 | No Data |
| | | 0.064 lb ai/gallon | | 2E-08 | 7E-09 | 6E-09 | 2E-08 | 5E-09 | 5E-09 | 2E-08 | 5E-09 | 4E-09 | No Data |
| | | 0.03 lb ai/gallon | | 9E-08 | 3E-08 | 3E-08 | 8E-08 | 2E-08 | 2E-08 | 8E-08 | 2E-08 | 2E-08 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 1E-09 | 7E-10 | 7E-10 | 6E-10 | 2E-10 | 2E-10 | 6E-10 | 1E-10 | 1E-10 | No Data |
| | | 0.00077 lb ai/animal | | 6E-10 | 3E-10 | 3E-10 | 3E-10 | 9E-11 | 9E-11 | 3E-10 | 6E-11 | 6E-11 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 2E-08 | 1E-08 | 1E-08 | 9E-09 | 3E-09 | 3E-09 | 8E-09 | 2E-09 | 2E-09 | No Data |
| | | 0.0017 lb ai/animal | | 1E-08 | 7E-09 | 7E-09 | 7E-09 | 2E-09 | 2E-09 | 7E-09 | 1E-09 | 1E-09 | No Data |

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| Table L.2. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Private/Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 3E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 3E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 | 20,000 birds | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00032 | 20,000 | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.2. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Private/Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | lb ai/sq ft | sq ft | | | | | | | | | | |
| | | 0.00016 lb ai/sq ft | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Mixer/Loader/Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-06 | 7E-07 | 6E-07 | 1E-06 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 2E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 6E-06 | 4E-06 | 3E-06 | 5E-06 | 2E-06 | 1E-06 | 5E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 | 20,000 birds | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 3E-06 | 1E-06 | 1E-06 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 7E-07 | 4E-07 | No Data |
| | | 0.00016 lb ai/sq ft | | 1E-06 | 7E-07 | 6E-07 | 1E-06 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 2E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | 100,000 (sq ft/day) | 2E-06 | 3E-07 | 2E-07 | 2E-06 | 3E-07 | 2E-07 | 2E-06 | 3E-07 | 2E-07 | 7E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | 6E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 5E-08 | 4E-08 | 1E-08 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 1E-07 | 2E-08 | 2E-08 | 1E-07 | 2E-08 | 2E-08 | 1E-07 | 2E-08 | 2E-08 | 6E-09 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 3E-09 | 6E-10 | 4E-10 | 3E-09 | 5E-10 | 4E-10 | 3E-09 | 5E-10 | 4E-10 | 1E-10 |
| | | 0.064 lb ai/gallon | | 3E-09 | 5E-10 | 4E-10 | 3E-09 | 5E-10 | 3E-10 | 3E-09 | 4E-10 | 3E-10 | 1E-10 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 2E-06 | 1E-06 | 9E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 1E-05 | 2E-06 | 2E-06 | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 6E-07 | 5E-07 | 4E-08 |
| (2b) Mixing/ Loading | | 0.080 lb ai/gallon | 2 gallons | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 1E-09 | 1E-09 | 2E-08 | 1E-09 | 1E-09 | 7E-11 |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Wettable Powders for Paint Applications | Poultry (Floor Management – Roost) | | | | | | | | | | | | |
| (3a) Mixing/ Loading Dusts for Paint Applications (WP Data as Surrogate) | | 0.030 lb ai/gallon | | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 1E-09 | 1E-09 | 2E-08 | 1E-09 | 1E-09 | 7E-11 |
| **Applicators** | | | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 1E-07 | 4E-08 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 9E-08 | 6E-07 | 1E-07 | 9E-08 | 4E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 5E-07 | 1E-07 | 1E-07 | 5E-07 | 1E-07 | 8E-08 | 5E-07 | 1E-07 | 8E-08 | 3E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 2E-07 | 6E-08 | 5E-08 | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 5E-08 | 4E-08 | 2E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 1E-07 | 2E-08 | 2E-08 | 9E-08 | 2E-08 | 2E-08 | 9E-08 | 2E-08 | 2E-08 | 7E-09 |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 5E-08 | 1E-08 | 1E-08 | 5E-08 | 1E-08 | 8E-09 | 5E-08 | 1E-08 | 8E-09 | 3E-09 |
| (5) Open Pour Liquid Additive for Feed Through Applications | Cattle Feed (Concentrate) | 0.0039 lb ai/animal | 1,000 cows | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 5E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | No Data |
| | Horse Feed | 0.0017 lb ai/animal | 500 horses | 2E-08 | 3E-09 | 2E-09 | 2E-08 | 3E-09 | 2E-09 | 2E-08 | 3E-09 | 2E-09 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| (6a) RTU Pet Collar Applications – 1/99 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 7E-07 | 5E-07 | 2E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 1E-06 | 8E-07 | 3E-05 | 9E-07 | 7E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 1E-05 | 1E-06 | 9E-07 | 1E-05 | 5E-07 | 4E-07 | 1E-05 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 6E-07 | 4E-07 | 2E-05 | 5E-07 | 4E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 2E-05 | 2E-06 | 1E-06 | 2E-05 | 9E-07 | 6E-07 | 2E-05 | 8E-07 | 5E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 7E-07 | 5E-07 | 2E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 1E-06 | 8E-07 | 3E-05 | 9E-07 | 7E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 9E-06 | 3E-07 | 3E-07 | 9E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 5E-05 | 3E-06 | 3E-06 | 5E-05 | 2E-06 | 1E-06 | 5E-05 | 2E-06 | 1E-06 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 2E-05 | 2E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 1E-05 | 1E-06 | 8E-07 | 1E-05 | 5E-07 | 4E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| (6b) RTU Pet Collar Applications - 50/50 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 6E-06 | 5E-07 | 4E-07 | 6E-06 | 3E-07 | 2E-07 | 6E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 9E-06 | 5E-07 | 3E-07 | 9E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 8E-06 | 6E-07 | 5E-07 | 7E-06 | 4E-07 | 3E-07 | 7E-06 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 9E-06 | 7E-07 | 6E-07 | 9E-06 | 4E-07 | 3E-07 | 8E-06 | 4E-07 | 3E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 6E-06 | 5E-07 | 4E-07 | 6E-06 | 3E-07 | 2E-07 | 6E-06 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 1E-05 | 1E-06 | 9E-07 | 1E-05 | 6E-07 | 4E-07 | 1E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 9E-06 | 5E-07 | 3E-07 | 9E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 2E-05 | 1E-06 | 9E-07 | 2E-05 | 1E-06 | 8E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 1E-05 | 1E-06 | 8E-07 | 1E-05 | 6E-07 | 4E-07 | 1E-05 | 5E-07 | 4E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 7E-06 | 6E-07 | 5E-07 | 7E-06 | 4E-07 | 3E-07 | 7E-06 | 3E-07 | 2E-07 | No Data |
| (6c) RTU Pet Collar Applications - 99/1 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 5E-07 | 2E-07 | 2E-07 | 5E-07 | 2E-07 | 2E-07 | 5E-07 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 8E-07 | 5E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 8E-07 | 4E-07 | 2E-07 | 8E-07 | 4E-07 | 2E-07 | 8E-07 | 4E-07 | 2E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| Mixers/Loaders/Applicators | | | | | | | | | | | | | |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | | 0.032 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | | 0.0013 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 4E-07 | 4E-07 | 3E-07 | 4E-07 | 4E-07 | 2E-07 | 4E-07 | 4E-07 | 2E-07 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | No Data |
| (9b) Liquid: | | 0.039 | 400 | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Manually-Pressurized Handwand | Beef Cattle - Direct Applied | lb ai/animal | animals | | | | | | | | | | |
| | | 0.032 lb ai/animal | | 1E-04 | 9E-07 | 8E-07 | 1E-04 | 6E-07 | 5E-07 | 1E-04 | 5E-07 | 5E-07 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 3E-04 | 2E-06 | 2E-06 | 3E-04 | 1E-06 | 1E-06 | 3E-04 | 1E-06 | 1E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 1E-04 | 7E-07 | 7E-07 | 1E-04 | 5E-07 | 4E-07 | 1E-04 | 4E-07 | 4E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 2E-04 | 1E-06 | 1E-06 | 2E-04 | 9E-07 | 8E-07 | 2E-04 | 8E-07 | 7E-07 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 9E-08 | 8E-08 | 2E-05 | 8E-08 | 7E-08 | No Data |
| | | 0.0013 lb ai/animal | | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-04 | 9E-07 | 8E-07 | 1E-04 | 6E-07 | 5E-07 | 1E-04 | 5E-07 | 5E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 9E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-05 | 1E-07 | 1E-07 | 1E-05 | 7E-08 | 6E-08 | 1E-05 | 7E-08 | 6E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-05 | 9E-08 | 8E-08 | 1E-05 | 6E-08 | 5E-08 | 1E-05 | 5E-08 | 5E-08 | No Data |
| (9c) Liquid: | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Mechanically -Pressurized Handgun | | 0.032 lb ai/animal | | 3E-06 | 2E-06 | 1E-06 | 2E-06 | 9E-07 | 6E-07 | 2E-06 | 9E-07 | 5E-07 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.026 lb ai/animal | | 3E-06 | 1E-06 | 1E-06 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 7E-07 | 4E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 5E-06 | 3E-06 | 2E-06 | 4E-06 | 1E-06 | 1E-06 | 3E-06 | 1E-06 | 8E-07 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 5E-07 | 3E-07 | 2E-07 | 4E-07 | 1E-07 | 1E-07 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 1E-07 | 7E-08 | 6E-08 | 9E-08 | 4E-08 | 3E-08 | 9E-08 | 3E-08 | 2E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 6E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3E-06 | 2E-06 | 1E-06 | 2E-06 | 9E-07 | 6E-07 | 2E-06 | 9E-07 | 5E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-06 | 9E-07 | 7E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 4E-07 | 3E-07 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 4E-07 | 2E-07 | 2E-07 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 6E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 3E-07 | 2E-07 | 1E-07 | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 5E-08 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 gallons | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| | | 0.064 lb ai/gallon | | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| (10a) Wettable Powder: Backpack Sprayer | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | | 8E-07 | 8E-07 | 6E-07 | 8E-07 | 8E-07 | 5E-07 | 8E-07 | 7E-07 | 5E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 4E-07 | 4E-07 | 3E-07 | 4E-07 | 4E-07 | 2E-07 | 4E-07 | 4E-07 | 2E-07 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 1E-08 | 1E-08 | 7E-09 | 9E-09 | 9E-09 | 6E-09 | 9E-09 | 9E-09 | 6E-09 | No Data |
| (10b) Wettable | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Powder: Manually-Pressurized Handwand | Swine - Direct Spray | 0.020 lb ai/animal | | 7E-05 | 5E-07 | 5E-07 | 7E-05 | 4E-07 | 3E-07 | 7E-05 | 3E-07 | 3E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 7E-05 | 5E-07 | 5E-07 | 7E-05 | 4E-07 | 3E-07 | 7E-05 | 3E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | | 0.00016 lb ai/sq ft | | 3E-05 | 2E-07 | 2E-07 | 3E-05 | 1E-07 | 1E-07 | 3E-05 | 1E-07 | 1E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 1E-05 | 1E-07 | 1E-07 | 1E-05 | 7E-08 | 6E-08 | 1E-05 | 7E-08 | 6E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 4E-07 | 3E-09 | 3E-09 | 4E-07 | 2E-09 | 2E-09 | 4E-07 | 2E-09 | 1E-09 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 3E-04 | 3E-04 | 3E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 7E-04 | 7E-04 | 7E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 2E-04 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Plunger Data as Surrogate) | | | | | | | | | | | | | |
| (10f) Wettable Powder: Plunger Duster (Dust Data as Surrogate) | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 3E-05 | 6E-06 | 6E-06 | 3E-05 | 4E-06 | 4E-06 | 2E-05 | 4E-06 | 3E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 1E-05 | 3E-06 | 3E-06 | 1E-05 | 2E-06 | 2E-06 | 1E-05 | 2E-06 | 2E-06 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 4E-06 | 9E-07 | 8E-07 | 4E-06 | 6E-07 | 5E-07 | 4E-06 | 6E-07 | 5E-07 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 1E-04 | 3E-05 | 3E-05 | 1E-04 | 2E-05 | 2E-05 | 1E-04 | 2E-05 | 2E-05 | No Data |
| | | 0.38 lb ai/dust bag | | 6E-05 | 1E-05 | 1E-05 | 6E-05 | 1E-05 | 9E-06 | 6E-05 | 9E-06 | 8E-06 | No Data |
| | | 0.13 lb ai/dust bag | | 2E-05 | 5E-06 | 5E-06 | 2E-05 | 3E-06 | 3E-06 | 2E-05 | 3E-06 | 3E-06 | No Data |
| (11b) Dust: Shaker Can (Plunger Data Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 1E-03 | 8E-05 | 7E-05 | 1E-03 | 4E-05 | 3E-05 | 1E-03 | 4E-05 | 3E-05 | No Data |
| | | 0.0038 lb ai/animal | | 6E-04 | 4E-05 | 4E-05 | 6E-04 | 2E-05 | 2E-05 | 6E-04 | 2E-05 | 1E-05 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 2E-04 | 1E-05 | 1E-05 | 2E-04 | 7E-06 | 5E-06 | 2E-04 | 6E-06 | 4E-06 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/ bird | 1,000 birds | 2E-04 | 2E-05 | 1E-05 | 2E-04 | 8E-06 | 6E-06 | 2E-04 | 7E-06 | 5E-06 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 1E-04 | 8E-06 | 7E-06 | 1E-04 | 4E-06 | 3E-06 | 1E-04 | 4E-06 | 3E-06 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 8E-05 | 5E-06 | 5E-06 | 8E-05 | 3E-06 | 2E-06 | 8E-05 | 2E-06 | 2E-06 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 4E-05 | 3E-06 | 2E-06 | 4E-05 | 1E-06 | 1E-06 | 4E-05 | 1E-06 | 8E-07 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | | 0.0038 lb ai/animal | | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 5E-06 | 4E-06 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 8E-04 | 1E-04 | 1E-04 | 8E-04 | 1E-04 | 1E-04 | 8E-04 | 1E-04 | 1E-04 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 3E-06 | 4E-07 | 4E-07 | 3E-06 | 4E-07 | 3E-07 | 3E-06 | 4E-07 | 3E-07 | No Data |
| | | 0.077 lb ai/gallon | | 3E-06 | 4E-07 | 4E-07 | 3E-06 | 4E-07 | 3E-07 | 3E-06 | 3E-07 | 3E-07 | No Data |
| | | 0.064 lb ai/gallon | | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | No Data |
| | | 0.03 lb ai/gallon | | 1E-06 | 1E-07 | 1E-07 | 1E-06 | 1E-07 | 1E-07 | 1E-06 | 1E-07 | 1E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 7E-07 | 3E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | No Data |
| | | 0.077 lb ai/gallon | | 7E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | No Data |
| | | 0.064 lb ai/gallon | | 6E-08 | 2E-08 | 2E-08 | 5E-08 | 2E-08 | 1E-08 | 5E-08 | 1E-08 | 1E-08 | No Data |
| | | 0.03 lb ai/gallon | | 3E-07 | 1E-07 | 9E-08 | 2E-07 | 7E-08 | 7E-08 | 2E-07 | 7E-08 | 6E-08 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 3E-09 | 2E-09 | 2E-09 | 2E-09 | 5E-10 | 5E-10 | 2E-09 | 3E-10 | 3E-10 | No Data |
| | | 0.00077 lb ai/animal | | 2E-09 | 1E-09 | 1E-09 | 1E-09 | 3E-10 | 3E-10 | 9E-10 | 2E-10 | 2E-10 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 5E-08 | 3E-08 | 3E-08 | 3E-08 | 8E-09 | 8E-09 | 3E-08 | 5E-09 | 5E-09 | No Data |
| | | 0.0017 lb ai/animal | | 4E-08 | 2E-08 | 2E-08 | 2E-08 | 6E-09 | 6E-09 | 2E-08 | 4E-09 | 4E-09 | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (10c) Wettable Powder: | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 5E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 7E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 3E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loader/Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 7E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 2E-05 | 1E-05 | 9E-06 | 1E-05 | 6E-06 | 4E-06 | 1E-05 | 5E-06 | 3E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 8E-06 | 4E-06 | 4E-06 | 6E-06 | 2E-06 | 2E-06 | 6E-06 | 2E-06 | 1E-06 | No Data |
| | | 0.00016 lb ai/sq ft | | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 7E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |

Appointment

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/16/2017 5:14:49 PM
**To**: Parker, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f2d8b49ca67a44218a01d83521029f67-James Parker]; Nguyen, Khue [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53463f4f956d4772a6ada2f68debfcb8-Nguyen, Khue]; Biggio, Patricia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2a9a640a9a2941c5a9be1c4967e71718-Biggio, Pat]
**BCC**: DCRoomPYS9671/Potomac-Yard-One [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=user18c48aa6]

**Subject**: Tetrachlorvinphos HED Revised Risk Assessment Discussion
**Attachments**: TCVP revised human health assessment dec2016.pdf; TCVP PID Mitigation Proposal 1.10.17.docx; TCVP RA one-pager 1.31.17..docx
**Location**: DCRoomPYS9671/Potomac-Yard-One

**Start**: 2/16/2017 9:00:00 PM
**End**: 2/16/2017 9:30:00 PM
**Show Time As**: Busy

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM**

**Date:** December 21, 2016

**SUBJECT:** **Tetrachlorvinphos (TCVP)** Revised Human Health Risk Assessment for Registration Review

**PC Code:** 083701, 083702
**Petition No.:** NA
**Risk Assessment Type:** Single Chemical Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** 436834
**Registration Nos.:** NA
**Regulatory Action:** Registration Review
**Case No.:** 1321
**CAS No.:** 22248-79-9
**40 CFR:** §180.252

**FROM:** Danette Drew, Chemist
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Health Effects Division (HED, 7509P)

**TO:** James Parker, Chemical Review Manager
Neil Anderson, Branch Chief
Risk Management and Implementation Branch I
Pesticide Re-evaluation Division (7508P)

Attached is HED's revised human health risk assessment in support of the registration review of the insecticide tetrachlorvinphos (TCVP).



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## 1.0 Executive Summary

The insecticide tetrachlorvinphos (TCVP) [(Z)-2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate] is a member of the organophosphate (OP) class of pesticides. TCVP is used as a dermal or oral treatment to livestock (i.e., cattle, swine, poultry and horses) and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs. Formulations for pet use include collars, dusts/powders, and pump and trigger sprays. The other (non-pet) uses include dusts (D), emulsifiable concentrates (EC), feed through (solid and liquid food additives), feed blocks, and wettable powders (WP). Human exposure to TCVP in food may occur as a result of consuming residues in animal commodities (e.g., meat). Exposure may also occur from drinking water that may contain TCVP residues as a result of some outdoor use patterns. Residential exposures may occur as a result of applying flea products to pets (cats and dogs) or contacting treated pets. Occupational exposures may occur during application of TCVP to livestock or their premises, or during outdoor perimeter or kennel treatments. Occupational exposures may also occur to veterinarians and pet groomers. Exposure via spray drift is not anticipated based on the current use patterns.

The most recent human health risk assessment for TCVP was completed in December 2015 (D. Drew *et al.*, 12/21/2015, *Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review*, D411095). The current TCVP risk assessment reflects the following changes since the 2015 risk assessment:

- The reduction of the oral toxicological point of departure (POD) from 8.0 mg/kg/day to 2.8 mg/kg/day based on additional red blood cell (RBC) acetylcholinesterase (AChE) inhibition data identified during this re-evaluation in the current acute comparative cholinesterase assay (CCA) study in rats.

- The use of the literature study, Davis, M. et al., *Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos.* Journal of Exposure Science and Environmental Epidemiology ((2008) 18, 564-57), (*hereinafter* Davis study), following approval for its use in risk assessment by the Human Studies Review Board (HSRB) in January 2016. Previously, risk estimates from both a surrogate residue transfer study (i.e., an amitraz pet collar study[1]) and the Davis literature study were presented. HED is now relying solely on the Davis study data since these chemical-specific data have been approved by the HSRB for use and result in a higher estimated exposure potential (i.e., are more health protective) than the surrogate data.

- Following a reassessment of the mutagenicity data available on TCVP, the relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be

[1] MRID 49468801: *Determination of Transferable Residues of Amitraz from the Hair of Dogs Following the Application of the Preventic® Collar.*

established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[2].

- Following the Dec. 21, 2015 TCVP risk assessment, information was submitted during the public comment period to address whether the active ingredients in TCVP pet collars are released as a liquid or solid (dust) form, or both. The submitted information describes that both a liquid and particulate, or dust, are present on the surface of the pet collar. Therefore, HED has assumed that TCVP could be transferred in either form from the collar to the pet's fur and result in the potential for post-application exposures from contact with the treated pet. HED has assessed exposures resulting from the TCVP pet collar uses assuming that the TCVP pet collar product exists as a liquid and solid form concurrently at varying ratios (e.g., 1/99, 50/50, and 99/1 liquid/dust). [See Section 6.0 of this document for a complete description of this approach].

This document also addresses, where appropriate, the comments received during the public comment period following publication of the 2015 TCVP draft human health risk assessment. A comprehensive response to comments received is also provided in the following memo: D. Drew et al., *Tetrachlorvinphos (TCVP) Health Effects Division Response to Comments on the December 21, 2015 Draft Human Health Risk Assessment for TCVP Registration Review*, D433403, 12/21/2016).

*Hazard*

TCVP is a member of the OP class of pesticides. For TCVP, like other OPs, the initiating event in the adverse outcome pathway/mode of action (AOP/MOA) involves inhibition of the enzyme acetylcholinesterase (AChE) *via* phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For TCVP, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. TCVP does not require metabolic activation to an oxon to inhibit AChE; i.e., the parent compound is the active form inhibiting AChE. OPs generally exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same dose, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks; a pattern that is observed for most OPs, but not every OP, like TCVP, which shows no difference in response across duration. For TCVP the steady state is

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[2] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.



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reached after a single day of exposure. As such, the endpoint selection for TCVP considers data available for all durations of dosing when choosing the most protective point of departure.

The toxicology database for TCVP is complete except the requirement for additional mutagenicity studies [a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and an assay that examines possible genotoxic activity in the target (liver) organ] (McCarroll, 2016; TXR No. 0057226)[3]. TCVP has cholinesterase data across multiple lifestages, durations, and routes for both red blood cell (RBC) and brain cholinesterase inhibition. There are acceptable studies available for toxicity endpoint and point of departure (POD) selection. For TCVP, RBC AChE inhibition is the most sensitive endpoint and is the endpoint from which the PODs for all TCVP exposure routes and durations were selected.

There is no evidence of quantitative or qualitative sensitivity in the developmental rat and rabbit studies or in the gestational (fetus) or juvenile components of the comparative cholinesterase assay (CCA) studies in rats. AChE data from the CCA studies suggest that the fetus is not more sensitive than the pregnant dam, and that pregnant females are not more sensitive than non-pregnant females with respect to cholinesterase inhibition. When comparing RBC $BMD_{10}$ (benchmark dose) estimates from across the acute (single dose) CCA and repeat dose CCA studies, it is apparent that there are no age-related (or duration-related) differences. The acute and steady state PODs selected for oral exposure risk assessment are based on RBC AChE inhibition in the postnatal day 11 (PND11) and postnatal day 21 (PND21) pups in the acute CCA since they provide the most robust dose-responses and are protective of all life stages. Although the steady state dietary POD was selected from an acute CCA, the acute study is considered appropriate for longer term durations since AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose.

High quality AChE data for the dermal and inhalation routes are also available and allow for route specific evaluation. RBC AChE inhibition was observed in both sexes in the inhalation study (brain AChE was not assessed), while no inhibition of RBC or brain AChE was observed in the dermal study up to the limit dose. A non-cancer dermal assessment is not required for TCVP; however, a cancer dermal assessment is required. The dermal absorption factor is 9.6% for TCVP.

TCVP is classified as a Group C possible human carcinogen (based on statistically significant increases in combined hepatocellular adenoma/carcinoma in female mice) with a linear low-dose approach for quantification of risk using the oral slope factor (Q1*) of $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$. Whereas parent compound TCVP is the residue of concern for AChE inhibition, TCVP plus metabolites containing the 2,4,5 trichlorobenzene moiety are the residues of concern for cancer assessment. Following a reassessment of the mutagenicity data available on TCVP, it was determined that the relevance of the mutagenic findings to the tumorigenic response seen in

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[3] *Ibid.*



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female mice cannot be established. Following the submission and review of the required mutagenicity assays, the need for an updated cancer assessment will be determined.

For TCVP, as for other OPs, the FQPA safety factor (SF) of 10X has been retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

For the acute and steady state dietary assessments, a total uncertainty factor of 1000X is appropriate for infants, children, youths and females of childbearing age (10X to account for interspecies extrapolation and 10X for intraspecies variation and the 10X FQPA SF). The only population subgroup for dietary exposure scenarios for which the FQPA SF is not retained is adults 50-99 years of age; therefore, the total uncertainty factor for that population is 100X.

A total uncertainty factor of 1000X is appropriate for residential incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF). A total uncertainty factor of 300X is appropriate for all inhalation exposures: 3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments (or a 10X database uncertainty factor for occupational assessments to protect potentially pregnant female workers) due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

*Tolerances*

Tolerances for residues of TCVP are established under 40 CFR §180.252 for livestock commodities based on oral feed-through and direct dermal uses on livestock (cattle, swine, and poultry). The residues of concern for tolerance enforcement are tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol (frequently abbreviated as TCVP, TCVPdeme, TCPEol , TCPEone, and TCPEdiol, respectively). The current tolerance expression under 40 CFR §180.252 includes all of these residues except des-O-methyl tetrachlorvinphos; this metabolite should be included in the tolerance expression. The current tolerance levels should be updated in the 40 CFR as discussed in Section 2.2.3.
There are no Codex maximum residue limits (MRLs) established or proposed for residues of TCVP. Canada has established MRLs for plant (apple and grape) and livestock commodities. The differences in U.S. and Canadian residue definitions prohibit harmonization.

*Dietary Risk Assessment*

Acute (TCVP), steady state (TCVP), and cancer (TCVP plus metabolites containing the 2,4,5 trichlorobenzene moiety) dietary (food and drinking water) exposure and risk assessments were conducted using the DEEM-FCID v3.16 model. The dietary exposure analyses for TCVP are mostly refined. The only food forms included in the analyses are based on animal commodities. The food residues were based upon U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) monitoring data except where no appropriate PDP data were available (i.e.,



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residues from poultry dermal application studies were used for poultry fat and skin). The Biological and Economic Analysis Division (BEAD) of OPP provided percent of livestock treated information. Model-derived estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effect Division (EFED). A distribution of EDWCs was used probabilistically in the acute and steady state analyses. For the cancer analysis, the EDWC was included as a single point estimate.

The acute dietary (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 190% of the aPAD. When drinking water is analyzed by itself, the acute dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95$^{th}$ and 99.9$^{th}$ percentile of exposure.

The steady state (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the steady state population adjusted dose (ssPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 120% of the ssPAD. The steady state dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95$^{th}$ and 99.9$^{th}$ percentile of exposure.

*Residential Handler Risk Assessment*

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are assumed to complete all elements of an application without use of any protective equipment.

Residential TCVP handler exposures are anticipated to be short- (1 to 30 days) and intermediate-term (1 to 6 months) in duration. However, because of the steady state AChE inhibition exhibited by the OPs (typically 21 days and longer for OPs, but 1 day to reach steady state for TCVP), steady state exposures were assessed and presented for residential exposures to TCVP pet products. Residential handler exposures to TCVP pet products may occur via the dermal or inhalation routes while the product is placed on a cat or dog. Both steady state non-cancer and cancer residential handler exposure assessments were performed for adult homeowners applying TCVP pet collars, dusts/powders, and pump/trigger sprays products to cats and dogs. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are assessed.

<u>Residential Handler Steady State (Non-Cancer):</u>

Pet Collars: Because there is uncertainty as to whether the TCVP pet collars are liquid and/or dust formulated products, residential handler (adult) steady state inhalation exposures were evaluated assuming both liquid and dust residues are present simultaneously at varying ratios



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(e.g., 1/99, 50/50, and 99/1 liquid/dust). Unit exposure (UE) data (for handler exposure), and residue transfer data and transfer coefficients (for post-application exposure) specific to each formulation type were used. For handlers, the liquid formulation assessment used spot-on surrogate UE data, which assumes negligible inhalation exposure; therefore, only the dust-specific UE data (i.e., a TCVP dust/powder applicator exposure study) is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure. No non-cancer inhalation risks of concern were identified for residential handlers for any liquid/dust formulation ratio assumption (all MOEs ≥ level of concern (LOC) of 300). When assuming a ratio of 1/99 liquid/dust, MOEs range from 920 to 4,600; when assuming a ratio of 50/50 liquid/dust, MOEs range from 1,800 to 9,100; and when assuming a ratio of 99/1 liquid/dust, MOEs range from 91,000 to 450,000.

Dust/Powder and Pump/Trigger Spray: All residential handler (adult) non-cancer steady state inhalation risks estimated for the TCVP pet dust/powder and pump/trigger spray formulations are not of concern (i.e., all MOEs are > 300; LOC = 300; range = 3,200 to 160,000).

Residential Handler Cancer:

Pet Collars: Residential handler cancer risks (combined dermal and inhalation) estimated for TCVP pet collars assuming 1/99 and 50/50 liquid/dust formulation ratios are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$.

Dust/Powder and Pump/Trigger Spray: Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$.

*Residential Post-Application Risk Assessment*

There is the potential for post-application exposure for individuals exposed as a result of contacting a cat or dog previously treated with TCVP pet products (dusts/powders, pump/trigger sprays, pet collars). Since there is no non-cancer dermal hazard for TCVP, a quantitative non-cancer post-application dermal exposure assessment was not performed for adults or children. A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from applications to pets. The quantitative exposure/risk assessment for residential post-application exposures is based on incidental oral (hand-to-mouth) exposure to children (1 to < 2 years old) from contacting cats and dogs treated with TCVP. While not the only lifestage potentially exposed for these post-application scenarios, this lifestage is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential TCVP post-application exposures are anticipated to be short- (1 to 30 days), intermediate-term (1 to 6 months), and long-term (>6 months – *for pet collar scenarios only*) in duration. However, because of the steady state AChE inhibition exhibited by the OPs, steady state exposures were assessed and presented for residential exposures to TCVP pet products.

Residential Post-Application Steady State (Non-Cancer):

Pet Collars: As was done for residential handlers, due to the uncertainty as to whether the TCVP pet collars are liquid and/or dust formulated products, residential post-application exposures were evaluated assuming both liquid and dust residues are present simultaneously at varying ratios (e.g., 1/99, 50/50, and 99/1 liquid/dust). For post-application exposure from pet collars, the same data were used to estimate transferable residues for both liquid and dust formulations; however, the transfer coefficients used to assess potential post-application exposure to dust formulations are much higher compared to those used for liquid formulations. Therefore, as with handlers, the post-application risk estimates are driven by the presence of dust in the formulations. Children's incidental oral (hand-to-mouth) steady state exposures to pets treated with TCVP collars are estimated to be of concern regardless of the ratio of liquid/dust assumed (i.e., MOEs < 1000; LOC = 1000). When assuming a 1/99 liquid/dust formulation ratio, MOEs range from 0.91 to 7.4. When assuming a 50/50 liquid/dust formulation, MOEs range from 1.8 to 15, and when assuming a 99/1 liquid/dust formulation, MOEs range from 65 to 530.

Dust/Powder and Pump/Trigger Spray: Children's incidental oral (hand-to-mouth) steady state exposures to pets treated with TCVP dust/powders are estimated to be of concern (MOEs range from 98 to 640; LOC = 1000). However, children incidental oral exposures to pets treated with TCVP pump/trigger spray products are estimated not to be of concern (i.e., MOEs are > 1000; MOEs range from 1,600 to 15,000).

Residential Post-Application (Cancer):

Pet Collars: Residential post-application cancer (adult; dermal only as post-application inhalation exposure is negligible for this use) risk estimates for TCVP pet collars assuming 1/99 or 50/50 liquid/dust formulation ratios range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1 liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$.

Dust/Powder and Pump/Trigger Spray: Residential post-application cancer (adult; combined dermal and inhalation) risks estimated for TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$.

*Spray Drift*

A quantitative spray drift assessment was not conducted because the use of TCVP for direct animal treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs are either 1) not applied via aircraft, groundboom, or airblast equipment or 2) for applications to poultry buildings with groundboom equipment, the use is indoors and not anticipated to be a significant source of spray drift.

*Aggregate Risk Assessment*

The acute aggregate risk assessment combines exposures to TCVP from food and drinking water. There are acute risk estimates of concern for food only; therefore, a quantitative acute aggregate

risk assessment was not conducted. The steady state aggregate assessment includes the steady state dietary (food and drinking water) and residential exposures. However, because there are risks of concern associated with both dietary (food) and residential exposure, a quantitative steady state aggregate risk assessment was not conducted. If mitigation occurs such that the risks for the individual contributors to the aggregate risk are acceptable, a quantitative assessment may be completed at that time.

The cancer aggregate risk assessment combines residential and dietary (food and drinking water) expected lifetime exposures for adults. For TCVP, a cancer aggregate assessment was performed for adult handlers and for adult post-application activities related to residential pet product use.

The residential handler cancer aggregate assessment uses exposures from applying TCVP products to pets. The cancer aggregate assessment combines the highest (worst case, upper bound) handler exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type. The cancer aggregate (dietary and residential exposures) risk estimates for handlers for the upper bound exposures for collars, dust/powders, and pump/trigger sprays are in the $10^{-7}$ to $10^{-6}$ range

The residential post-application cancer aggregate assessment uses exposures from contacting pets treated with TCVP products. The cancer aggregate assessment combines the highest (worst case, upper bound) post-application exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type. The cancer aggregate (dietary and residential exposures) post-application risk estimates for the upper bound exposures for collars, dust/powders, and pump/trigger sprays range from $10^{-6}$ to $10^{-4}$.

*Occupational Handler Risk Assessment*

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. Occupational handler exposures to TCVP may occur via the dermal or inhalation routes while the mixing/loading and applying products registered for dermal or oral treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs (professional pet handlers).

Occupational handler exposure is expected to be short- and intermediate-term in duration. However, because of the steady state AChE inhibition exhibited by the OPs, steady state exposures were assessed and presented for occupational exposures to TCVP products. Both steady state non-cancer and cancer handler exposure assessments were performed. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment

includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are assessed.

Occupational Handler Steady State (Non-Cancer):

Of the 198 total occupational handler exposure scenarios assessed, the majority (162) are not of concern (i.e., steady state inhalation MOEs are $\geq 300$; LOC = 300) with currently required personal protective equipment (PPE) (i.e., respiratory protection). Of the remaining 36 handler exposure scenarios, an additional 25 are not of concern with consideration of increasing levels of respiratory protection (i.e., 11 occupational handler exposure scenarios result in estimated risks of concern despite the addition of respiratory protection or engineering controls).

Occupational Handler Cancer:

Occupational cancer risks were estimated for both private/farmer and contract/commercial handlers. Cancer risk estimates, with currently required PPE, range from $10^{-10}$ to $10^{-5}$ for private/farmer handlers and from $10^{-10}$ to $10^{-4}$ for contract/commercial handlers.

*Occupational Post-Application Risk Assessment*

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties.

Occupational post-application exposures are not anticipated for TCVP as the majority of application scenarios are not to foliar surfaces. The use of TCVP outdoors as a perimeter treatment is not expected to result in occupational post-application exposure as reentry activities related to crop production (e.g., scouting, harvesting) are not anticipated for this use pattern.

*Human Studies Review*

This risk assessment relies in part on data from studies in which human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from Pesticide Handler Exposure Database (PHED) 1.1; the AHETF database; the Residential SOPs (Treated Pets); as well as a TCVP dust/powder applicator exposure study (MRID 45519601), a mixer/loader/applicator wettable powder study (MRID 42622301), and TCVP dust and pump spray study (MRID 45485501): (1) are subject to ethics review pursuant to 40 CFR Part 26, (2) have received the review necessary for consideration in this risk assessment, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have

included review by the HSRB. Descriptions of data sources, as well as guidance on their use, can be found at the agency website.[4]

Data were also used from a literature study using TCVP pet collars, Davis, M. *et. al., Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos.* Journal of Exposure Science and Environmental Epidemiology. (2008) 18, 564-57). On January 12-13, 2016 the EPA HSRB met to address the scientific and ethical charge questions related to the Davis study. The HSRB concluded that, "the research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol used in the study can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars."[5]

*CropLife America Petition*

On November 29, 2016, CropLife America (CLA) submitted a petition to EPA asking the agency to "halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner." Any interim or final registration review decision for TCVP could potentially be impacted by EPA consideration of the epidemiological studies identified in the CLA petition. EPA is therefore placing a copy of the CLA petition in the registration review docket for TCVP. In the near future, EPA intends to publish a notice on its Pesticide Website announcing the receipt of the CLA petition and opening a comment period on the petition. Persons wishing to comment on the petition should respond to EPA in connection with that comment period.

## 2.0 HED Recommendations

### 2.1 Data Deficiencies

A follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and a study that investigates possible genotoxic activity in the target organ (liver) are required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target).

Based on the findings from the mutagenicity revisit, HED is recommending that TCVP be assayed in a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395)

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[4] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

[5] Letter from Liza Dawson, PhD, Chair of the EPA HSRB to Thomas Burke, PhD, MPH, EPA Science Advisor. Subject: January 12-13, 2016 EPA Human Studies Review Board Meeting Report. March 30, 2016.

using both sexes, an appropriate sample size (5/sex/dose/sacrifice time) and oral treatment (dietary would be the best fit for the risk assessment). HED further recommends that the assay should cover the range of doses used in the 1980 Hazleton study (MRID 00117443) that will span the tumorigenic dose range for both sexes and the conditions should simulate conditions in the Amer et al., 1983 study. An additional study which would investigate possible genotoxic activity in the target organ (*i.e.,* mouse liver) should be performed. This assay with the target tissue would be appropriate and should follow a similar protocol as described above and should examine DNA damage potential (*e.g.,* Comet assay, DNA adduct formation or any other DNA target)[6].

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

A gas liquid chromatography (GLC) method for the determination of TCVP *per se* in livestock commodities is described in the Pesticide Analytical Method (PAM), Vol. II, as Method I.

The registrant has submitted a method (14020.6106) for the determination of tetrachlorvinphos and its metabolites (TCVPdeme, TCPEdiol, TCPEone and TCPEol) in livestock commodities, which uses QuEChERS and LC/MS/MS methods. The test data for method 14020.6106 are classified as scientifically acceptable for use as an analytical method for ruminant and poultry commodities.

The submitted multiresidue method testing data are acceptable and indicate that FDA multiresidue methods are not suitable for analysis of the TCVP metabolites TCPEdiol and TCVPdeme. However, the metabolites TCPEol and TCPEone were recoverable under Protocol F, although fortified recoveries were small (<50%).

It should be noted that the FDA PESTDATA database dated 8/93 (PAM Vol. I, Appendix II) indicates that parent compound TCVP is completely recovered (>80%) using FDA multiresidue method protocol D (section 232.4) but is not recovered using protocol E (Sections 211.1/231.1 and 212.1/232.1, fatty and nonfatty matrices).

### 2.2.2 International Harmonization

There are no Codex maximum residue limits (MRLs) established or proposed for residues of TCVP. Canada has established MRLs for plant (apple and grape) and livestock commodities. The U.S. tolerances are for livestock commodities; there are no registered crop uses. Canada's residue definition is 2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate (TCVP) and its

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[6] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

low melting isomer as opposed to the U.S. definition which includes the parent compound TCVP plus the four metabolites of concern. The differences in U.S. and Canadian residue definitions prohibit harmonization. HED has not examined the Canadian registrations; different use patterns may also be a factor in achieving harmonization. A summary of U.S. and international tolerances and maximum residue limits is presented in Appendix F.

### 2.2.3 Recommended Tolerances

Tolerances for residues of TCVP in livestock commodities are established under 40 CFR §180.252. The current tolerance expression is for the combined residues of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] and its metabolites, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol.

The HED Metabolism Committee has determined that the residues of concern for tolerance enforcement are tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. The current tolerance expression under 40 CFR §180.252 includes all of these residues *except des-O-methyl tetrachlorvinphos*; this metabolite should be included in the tolerance expression. To allow separate risk assessments for 1) cholinesterase inhibition (parent TCVP only) and 2) carcinogenicity (parent plus metabolites), the tolerances for each livestock commodity should also specify the maximum residues of TCVP *per se* from the total residues. The tolerance definition should be modified as follows, to be consistent with the Tolerance Expression Guidance issued 5/27/09 (S. Knizner).

Tolerances are established for residues of the insecticide tetrachlorvinphos, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate) and its metabolites chloro- 1 -(2,4,5-trichlorophenyl)-vinylmonomethyl phosphate, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol, calculated as the stoichiometric equivalent of tetrachlorvinphos, in or on the commodity.

**Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos.**

| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
|---|---|---|---|---|
| Cattle, fat (of which no more than 0.1 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat | 1.0 | *Cattle, fat (of which no more than 0.6 ppm is tetrachlorvinphos per se)* |

| Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos. | | | | |
|---|---|---|---|---|
| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
| Cattle, kidney (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 1.0 | -- | Remove | See cattle, meat byproducts |
| Cattle, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.5 | -- | Remove | |
| Cattle, meat (of which no more than 2.0 ppm is tetrachlorvinphos *per se*) | 2.0 | 0.27 (0.21) muscle | 0.3 | *Cattle, meat (of which no more than 0.2 ppm is tetrachlorvinphos per se)* |
| Cattle, meat by products, except kidney and liver | 1.0 | -- | Remove | See cattle, meat byproducts |
| Cattle, meat by products | None | 0.16 (<0.01) liver; 0.28 (0.015) kidney; 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat; 0.27 (0.21) muscle | 1.0 | *Cattle, meat byproducts (of which no more than 0.6 ppm is tetrachlorvinphos per se)* [5] |
| Egg (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.288 (0.026) | 0.3 | *Egg (of which no more than 0.03 ppm is tetrachlorvinphos per se)* |
| Hog, fat (of which no more than 0.1 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat | 1.0 | *Hog, fat (of which no more than 0.6 ppm is tetrachlorvinphos per se)* |
| Hog, kidney (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 1.0 | -- | Remove | See hog, meat byproducts |
| Hog, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.5 | -- | Remove | |
| Hog, meat (of which no more than 2.0 ppm is tetrachlorvinphos *per se*) | 2.0 | 0.27 (0.21) muscle | 0.3 | *Hog, meat (of which no more than 0.2 ppm is tetrachlorvinphos per se)* |
| Hog, meat byproducts, except kidney and liver | 1.0 | -- | Remove | See hog, meat byproducts |
| Hog, meat by products | None | 0.16 (<0.01) liver; 0.28 (0.015) kidney; 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat; 0.27 (0.21) muscle | 1.0 | *Hog, meat byproducts (of which no more than 0.6 ppm is tetrachlorvinphos per se)* [5] |

| Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos. | | | | |
|---|---|---|---|---|
| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
| Milk, fat (reflecting negligible residues in whole milk and of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.05 | 0.072 (0.036) for milk; 0.078 (<0.01) for cream | 0.1 | *Milk (of which no more than 0.04 ppm is tetrachlorvinphos per se)* |
| Poultry, fat (of which no more than 7.0 ppm is tetrachlorvinphos *per se*) | 7.0 | 1.298 (0.099) abdominal fat | 1.4 | *Poultry, fat (of which no more than 0.1 ppm is tetrachlorvinphos per se)* |
| Poultry, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 2.0 | | Remove | See poultry, meat byproducts |
| Poultry, meat (of which no more than 3.0 ppm is tetrachlorvinphos *per se*) | 3.0 | 0.40 (0.082) muscle | 0.4 | *Poultry, meat (of which no more than 0.1 ppm is tetrachlorvinphos per se)* |
| Poultry, meat byproducts, except liver | 2.0 | -- | Remove | See poultry, meat byproducts |
| Poultry, meat byproducts | None | 0.52 (0.016) liver; 0.58 (0.022) kidney; 0.40 (0.082) muscle; 19.41 (6.03) skin with fat; 1.30 (0.099) abdominal fat | 20 | *Poultry, meat byproducts (of which no more than 6.0 ppm is tetrachlorvinphos per se)* [5] |

[1] Time-limited tolerances; current tolerance expression is for the combined residues of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] and its metabolites, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol; expression should also include des-O-methyl tetrachlorvinphos.

[2] Total residues of tetrachlorvinphos and its metabolites, TCVP-deme, TCPEone, TCPEol (free and conjugated forms), and TCPEdiol (free and conjugated), expressed in terms of parent equivalents; the value in parentheses represents the maximum residues of the parent tetrachlorvinphos.

[3] Reassessed tolerance is based on the maximum residue from the respective magnitude of the residue study; the maximum residues of the parent tetrachlorvinphos are reported in the corrected commodity definition.

[4] The residue data for cattle can be used to set tolerances for hog commodities since residues in hog tissues are not likely to be greater than those in cattle tissues.

[5] According to the 18 July 2007 Minutes of the HED ChemSAC meeting, the guidance document will be revised to include language detailing the use of the highest residue data for any tissue (liver, kidney, fat, skin or muscle) to determine the tolerance for meat byproducts. A single tolerance on "meat byproducts" will be recommended based on that highest residue, and individual tolerances will no longer be set on liver, kidney, or meat byproducts (except liver and kidney).

## 2.3 Label Recommendations

### 2.3.1 Recommendations from Residue Reviews



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The following label revisions are recommended based on the application methods and rates used in the tetrachlorvinphos magnitude of the residue studies, which were used to determine the appropriate tolerance levels in livestock commodities (GLN 860.1200 Directions for Use):

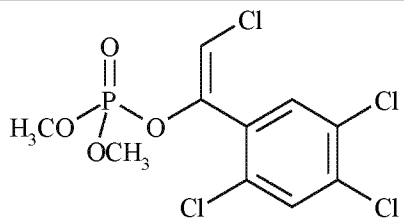
- Based on the magnitude of the residue study on cattle, the product labels with direct animal spray uses on cattle (EPA Reg. Nos. 61483-43 and 61483-50) should be amended to specify a maximum of three applications, with two-week retreatment intervals, at 19 g ai/animal/dose. The product label for Ravap (EPA Reg. No. 61483-50) should also be amended to provide conversion factors to allow calculation of direct animal spray treatment rate in terms of g ai/animal.

- Based on the magnitude of the residue study on poultry, the product labels with direct animal spray uses on poultry (EPA Reg. Nos. 61483-43 and 61483-50) should be amended to specify a maximum of seven applications (with two-week retreatment intervals) at 0.18 g ai/hen/application. Note that the label should specify the weight or volume of the product to be applied.

## 3.0 Introduction

### 3.1 Chemical Identity

**Table 3.1. Tetrachlorvinphos Nomenclature.**

| | |
|---|---|
| Compound |  |
| Common name | Tetrachlorvinphos |
| Company experimental name | TCVP |
| IUPAC name | (Z)-2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate |
| CAS registry number | 22248-79-9 |

See Appendices D and E for nomenclature and physical/chemical properties of TCVP and metabolites (TCVPdeme, TCPEdiol, TCPEone and TCPEol, TCCEol, TCBA).

### 3.2 Physical/Chemical Characteristics

Technical tetrachlorvinphos is a tan to brown crystalline solid with a melting point of 93-98 °C. TCVP is not expected to volatilize significantly due to a low vapor pressure of $2.6 \times 10^{-7}$ torr (25°C). The solubility of tetrachlorvinphos in water at 25°C is 11.6 mg/L. TCVP has limited solubility in most aromatic hydrocarbons. TCVP is hydrophobic, with an octanol-water partition coefficient of 3350 (Log $K_{ow}$ of 3.53).

### 3.3 Pesticide Use Pattern

TCVP is used as a direct animal treatment to livestock (i.e., cattle, horses, poultry and swine) and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs. The TCVP livestock and perimeter treatment uses are formulated as follows: dusts (D), emulsifiable concentrates (EC), feed through (solid, granular and pelleted/tableted) and liquid food additives), feed blocks, and wettable powders (WP). TCVP can be applied by a variety of means/equipment types including: backrubber/facerubber; backpack; cup; groundboom; handheld fogger; manually-pressurized handwand; mechanically-pressurized handwand; open pour (dust and liquid formulations); paint (airless sprayer or brush/roller); pet collar; plunger; rotary duster; shaker can; spoon; stationary fogger; and trigger spray. For a complete list of registered uses, including maximum use rates, see Appendix A of D436833 (W. Britton, 12/2016, *Tetrachlorvinphos: Final Occupational and Residential Exposure Assessment for Registration Review*).

### 3.4 Anticipated Exposure Pathways

Humans may be exposed to TCVP residues in food since TCVP may be directly applied to, or fed to, livestock which may result in residues in animal commodities. TCVP may reach surface and ground water sources of drinking water through the outdoor usage on poultry droppings, garbage and manure piles, and kennels and corrals. Residential exposures (handler and post-application) may occur as a result of the application to dogs and cats as dust/powders, sprays, or collars. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational post-application exposures are not expected as reentry activities are not anticipated for the registered TCVP uses.

### 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/environmentaljustice/resources/policy/exec_order_12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks

for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

## 4.0 Hazard Characterization and Dose-Response Assessment

TCVP is a member of the organophosphate class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway/mode of action (AOP/MOA) for TCVP involves inhibition of the enzyme AChE *via* phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). TCVP is in the oxon form and does not require bioactivation prior to inhibiting AChE. For TCVP, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating this toxicology database.

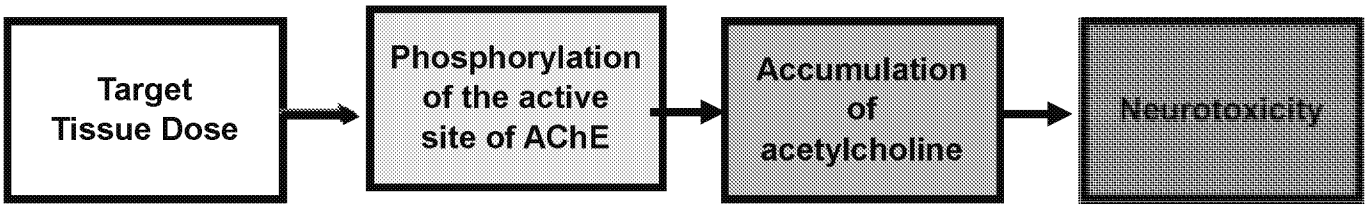



**Figure 1. Adverse outcome pathway for OPs**

### 4.1 Toxicology Studies Available for Analysis

The toxicology database for TCVP is complete except for a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and an *in vivo* assay to examine DNA damage potential (*e.g.,* Comet assay, DNA adduct formation, or any other DNA target)[7].

There are acceptable studies available for toxicity endpoint selection; they include:

- subchronic oral toxicity studies in rats
- chronic oral toxicity studies in rats and dogs
- carcinogenicity studies in rats and mice
- developmental studies in rats and rabbits
- reproduction study in rats

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[7] *Ibid.*

- acute and subchronic neurotoxicity studies in rats
- developmental neurotoxicity (DNT) study in rats
- acute and repeated comparative (CCA) cholinesterase (ChE) studies in juvenile and adult rats
- repeated, gestational ChE study in pregnant rats and fetuses
- delayed neurotoxicity study in hens
- subchronic dermal toxicity study in rats
- repeated dosing inhalation toxicity study in rats
- immunotoxicity study in mice
- complete mutagenicity study battery
- dermal penetration study in rats
- metabolism study in rats

## 4.2 Absorption, Distribution, Metabolism, & Excretion (ADME)

TCVP, unlike some other OPs, does not require metabolic activation to the oxon form to inhibit AChE. In a rat metabolism study, TCVP was almost completely metabolized, and most of the radiolabel was excreted in the urine (46%-60%) and feces (38%-56%) within 48 hours of dosing. Only minor amounts (>0.5%) were found in the tissues. Very little un-metabolized parent compound was recovered. The major metabolite in feces was trichlorophenylethanol, with lesser amounts of trichlorophenylethandiol. The major metabolite in urine was trichloromandelic acid, with lesser amounts of desmethyl tetrachlorvinphos. There is no evidence of bioaccumulation. Some differences in metabolism were noted between the sexes; *e.g.,* males excreted more trichloromandelic acid, a more completely metabolized form of TCVP, whereas females excreted more of the desmethyl TCVP, which could be derived from TCVP with only a single metabolic step.

### 4.2.1 Dermal Absorption

There is a dermal absorption study in rats, which provides a dermal absorption factor (DAF) of 9.6%. In an acceptable *in vivo* dermal penetration study in rats (MRID 42111501), male rats were treated at 0.01, 0.1, 1, and 5 mg/cm$^2$ and sacrificed at 0.5, 1, 2, 4, or 10 hours post dose. Based on total amount of radioactivity recovered from urine, tissues, feces, and carcass after 10 hours of dermal exposure, 84% of the applied dose (0.1 mg/cm$^2$) was recovered in the wash and 9.57% was in the skin, urine, feces, and carcass. The DAF was used to evaluate dermal exposures in the cancer risk assessment. However, since there was no dermal hazard identified for non-cancer endpoints in the dermal toxicity study on TCVP; *i.e.,* no AChE inhibition at the limit dose and no concern for increased susceptibility after repeat exposure, a quantitative dermal assessment was not performed (see Section 4.6.1).

## 4.3 Toxicological Effects



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AChE inhibition is the well-established cholinergic mode of action for OPs and is typically used as the critical effect in hazard characterization for members of this class of pesticides. TCVP inhibits AChE in various species including rats, mice, rabbits, and dogs and is the most sensitive effect in the database. TCVP has AChE data across multiple lifestages (fetal, post-natal, adult), durations (single to 104 weeks), and routes (oral, dermal, inhalation) for both red blood cell (RBC) and brain AChE inhibition. However, when looking at the AChE inhibition data across the numerous studies and datasets, it is apparent that there is no consistent pattern as to the relative sensitivity of the RBC and brain compartments, sex, or life stage. For instance, at a single dose of 10 mg/kg, male RBC and brain AChE were similarly inhibited in both adults (-17% and -13% respectively) and PND11 pups (-14% and -14%, respectively). Additionally, as is observed for some OPs, the oral AChE data demonstrate no increase in inhibition with repeated exposures as compared to a single dose. Specifically, the acute single dose CCA data show $BMD_{10}$ of 6.5, with the 11-day repeated exposure $BMD_{10}$ of 7.7 in adult male rats (see Section 4.3.2).

Transient clinical signs [gait alterations, constricted pupils, tremors (fore- and hindlimb), body cool to the touch, decreased defecation, red material on forelimbs, around eyes, nose, mouth] characteristic of cholinergic toxicity were observed in the acute neurotoxicity rat study, and tremors were observed in pregnant rats in the developmental toxicity study at dose levels 100X higher and 5X higher than those eliciting AChE inhibition, respectively. The hen study was negative for indications of delayed neurotoxicity.

There is no evidence of quantitative or qualitative sensitivity in the developmental rat and rabbit studies or in the rat reproduction study following pre-natal and/or postnatal exposure to TCVP. In the rat developmental toxicity study, no developmental effects were observed in the fetus. Developmental toxicity (increased early resorptions, post-implantation loss, and decreased number of live fetuses) was observed in the rabbit developmental toxicity study at the same dose level where significant toxicity (mortality, abortion) was observed in the maternal rabbit. No reproductive or offspring toxicity was observed in the 2-generation reproductive rat study, but increased adrenal weights were observed in the parental rats.

AChE data from the CCA study suggest that the fetus is not more sensitive than the pregnant dam, and that pregnant females are not more sensitive than non-pregnant females with respect to cholinesterase inhibition. When comparing RBC $BMD_{10}$ estimates from across the repeat (48773401) and acute studies (48773401a), it is apparent that there are no age-related (or duration-related) differences. For instance, the $BMD_{10}$ estimates range from 3.2 mg/kg in PND21 male rats to 5.0 mg/kg in PND11 male rats and to 6.5 mg/kg in adult males in the acute CCA study and from 8.6 mg/kg/day in adult female to 20.5 mg/kg/day in the PND 11 pups in the repeat CCA study. Furthermore, the points of departure (POD) used for risk assessment, which are based on cholinesterase inhibition in the PND11 and PND21 animals, since they provide the most robust BMD and BMDL dose-responses, are protective of all life stages.

In the developmental neurotoxicity study (DNT), quantitative susceptibility was observed in pups (decreased pup weight, decreased relative brain weight/measurements) but only at the high

dose of 200 mg/kg/day where maternal toxicity was not demonstrated. However, a 200 mg/kg/day dose to adult female rats in the repeat dose CCA study resulted in 62% RBC and 57% brain cholinesterase inhibition, indicating significant toxicity occurred in the dam in the DNT at this dose. The 200 mg/kg/day dose to the juvenile rats is 20-fold higher than doses reflecting approximately 10%-20% inhibition in juvenile pups in the CCA study and 70-fold higher than the point of departure. Therefore, when considered in combination with the results from the CCA, the high dose of the DNT is not of concern for risk assessment. The BMDs relied upon from the CCA study are protective of the effects observed in pups at higher doses in the DNT study.

TCVP is classified as a Group C possible human carcinogen with a linear low-dose approach for quantification of risk using the oral slope factor (Q1*) of $1.83 \times 10^{-3}$.

In acute lethality studies, TCVP has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is a slight dermal irritant, a moderate eye irritant, and a dermal sensitizer.

### 4.3.2 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined and focused on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute, single dosing, and repeated dosing studies in laboratory animals for TCVP. This analysis provides the basis for determining which exposure durations are appropriate for assessing the human health risk. Table 4.3.2.1 provides a summary of the representative results from experimental toxicology studies with TCVP.

**Table 4.3.2.1 – TCVP $BMD_{10}$ Results (mg/kg/day) for RBC and Brain AChE Inhibition Over Time in Adult Rats**

| MRID (study) | Days of Dosing | % inhibition at LOAEL (mg/kg) or the $BMD_{10}$ [1] | |
|---|---|---|---|
| | | **RBC** | |
| | | **Males** | **Females** |
| MRID 48773401a | 1 day | 10% at 6.5 ($BMD_{10}$) | 10% at 14.9 ($BMD_{10}$) |
| MRID 48773401 (repeat CCA) | 11 days | 10% at 7.7 ($BMD_{10}$) | 10% at 8.7 ($BMD_{10}$) |
| MRID 45570601 (21-day oral) | 21 days | No inhibition | 10% at 9.9 ($BMD_{10}$) |
| MRID 43371201 (90-day oral) | 90 days | 10% at 61.6 ($BMD_{10}$) | 10% at 10.5 ($BMD_{10}$) |
| MRID 42980901 (chronic oral) | 365 days | No inhibition | 29% at 63 |
| | | **Brain** | |

| Table 4.3.2.1 – TCVP $BMD_{10}$ Results (mg/kg/day) for RBC and Brain AChE Inhibition Over Time in Adult Rats | | | |
|---|---|---|---|
| **MRID (study)** | **Days of Dosing** | **% inhibition at LOAEL (mg/kg) or the $BMD_{10}$ [1]** | |
| | | **Males** | **Females** |
| MRID 48773401a | 1 day | 10% at 7.4 ($BMD_{10}$) | 10% at 11.6 ($BMD_{10}$) |
| MRID 48294601 (acute CCA) | 1 day | 10% at 6.8 ($BMD_{10}$) | 10% at 11.3 ($BMD_{10}$) |
| MRID 48773401 (repeat CCA) | 11 days | 10% at 33.8 ($BMD_{10}$) | 10% at 7.2 ($BMD_{10}$) |
| MRID 45570601 (21-day oral) | 21 days | No inhibition | 10% at 14.7 ($BMD_{10}$) |
| MRID 43371201 (90-day oral) | 90 days | No inhibition | 12% at 6.7 |
| MRID 42980901 (chronic oral) | 365 days | No inhibition | 14% at 63 |

[1]The BMD, not the BMDL, estimates are shown when available in Table 4.3.2.1. According to the BMD guidance, the central estimate (i.e., the BMD) is used for purposes of comparison. The LOAEL and percent inhibition is presented when a BMD estimate is not available.

In adults, OPs generally exhibit a phenomenon known as steady state cholinesterase (AChE) inhibition. After repeated dosing at the same dose, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks; a pattern that is observed for most OPs, but not every OP, like TCVP, which shows no difference in response across duration. For TCVP, the results in Table 4.3.2.1 show a similar response across durations suggesting that steady state is reached after a single day of exposure. Further, TCVP exhibits a shallow dose-response curve for cholinesterase inhibition; *i.e.*, large increases in administered dose result in only small changes in AChE inhibition, although this may be attributed to differences in time after dosing that the cholinesterase measurements were made. This shallow dose response leads to variability in the AChE data and a relatively broad range of values of3.2 to 61.6 mg/kg/day for $BMD_{10}$s and 2.8 to 26.3 mg/kg/day for $BMDL_{10}$s (Appendix B). Given the results in Table 4.3.2.1 for TCVP, single day and steady state durations should have the same point of departure for human health risk assessment. As such, the endpoint selection for TCVP considers data available for all durations of dosing when choosing a protective POD.

## 4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for TCVP. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised

draft human health risk assessment ((D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al., 12/29/2014). Initially, the agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[8]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years. For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP)

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[8] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170



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molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.-1; CDC, 2008)[9]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

**Table 4.4.1. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).**

| Pesticide | DMP | DMTP | DMDTP | DEP | DETP | DEDTP |
|---|---|---|---|---|---|---|
| Azinphos methyl | X | X | X | | | |
| Chlorethoxyphos | | | | X | X | |
| Chlorpyrifos | | | | X | X | |
| Chlorpyrifos methyl | X | X | | | | |
| Coumaphos | | | | X | X | |
| Dichlorvos (DDVP) | X | | | | | |
| Diazinon | | | | X | X | |
| Dicrotophos | X | | | | | |
| Dimethoate | X | X | X | | | |
| Disulfoton | | | | X | X | X |
| Ethion | | | | X | X | X |
| Fenitrothion | X | X | | | | |
| Fenthion | X | X | | | | |
| Isazaphos-methyl | X | X | | | | |
| Malathion | X | X | X | | | |
| Methidathion | X | X | X | | | |
| Methyl parathion | X | X | | | | |
| Naled | X | | | | | |
| Oxydemeton-methyl | X | X | | | | |
| Parathion | | | | X | X | |
| Phorate | | | | X | X | X |
| Phosmet | X | X | X | | | |
| Pirimiphos-methyl | X | X | | | | |
| Sulfotepp | | | | X | X | |
| Temephos | X | X | | | | |
| Terbufos | | | | X | X | X |
| Tetrachlorvinphos | X | | | | | |
| Trichlorfon | X | | | | | |

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

[9] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf



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For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al., 2008; Chen et al., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al., 2008; Chen et al., 2012; Racke et al., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al., 2008; Forsberg et al., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and Attention Deficit Hyperactivity Disorder (ADHD) were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] with additional support from a cross-sectional study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In

contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al. ,2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK-PD) model (D424485, D. Drew et al., 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[10] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children

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[10] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increase in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the TCVP human health risk assessment, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

### 4.5 Safety Factor for Infants and Children (FQPA Safety Factor)

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety Factor will be retained for TCVP for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.** [11]

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[11] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

### 4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for TCVP is complete and includes developmental toxicity studies in the rat and rabbit, a reproductive toxicity study in the rat, acute and subchronic neurotoxicity studies in the rat, a developmental neurotoxicity study in the rat, a three component comparative cholinesterase study in the rat (acute, repeat, and gestational exposure), and an acute delayed hen neurotoxicity study.

As discussed in Section 4.5, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

### 4.5.2 Evidence of Neurotoxicity

TCVP is an organophosphate insecticide with an established neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used to derive points of departure (PODs). Neurotoxicity related to inhibition of AChE by TCVP, which was noted in the ACN and rabbit developmental toxicity studies, included transient clinical signs characteristic of cholinergic toxicity and tremors, as discussed above. The points of departure selected for this risk assessment are protective of these clinical signs.

### 4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The concern for susceptibility is low based on the lack of susceptibility following *in utero* exposure to TCVP in either the rat or rabbit developmental toxicity study or following *in utero* and/or pre-/post-natal exposure to TCVP in the 2-generation reproduction rat study. The apparent quantitative susceptibility observed in pups in the DNT occurred at the same dose level where 60% RBC and 45% brain cholinesterase inhibition occurred in pups and 62% RBC and 57% brain inhibition occurred in the adult females in the repeat CCA study. This comparison demonstrates that significant inhibition and toxicity also occurred in the maternal rat in the DNT, and repeat dosing showed no sensitivity with respect to the magnitude of the cholinesterase inhibition between the dam and pups. Furthermore, the effects observed in the DNT occurred at a dose 70-fold higher than the point of departure (POD). The POD is based on the AChE data from PND11 and PND21 pups from the acute CCA study, which provided the lowest POD, and is protective of the effects observed in the DNT.

As discussed in Section 4.5, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

### 4.5.4 Residual Uncertainty in the Exposure Database



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There are no residual uncertainties in the exposure database. The mostly refined dietary risk assessment uses food residues levels from monitoring data and from empirical studies, percent livestock treated data and model-estimated drinking water concentrations from maximum application rates. Residential exposure assessments use data from surrogate and chemical-specific sources. The exposure assumptions will not underestimate risks.

## 4.6 Toxicology Endpoint and Point of Departure Selections

### 4.6.1 Dose-Response Assessment

Table 4.6.4.1 summarizes the TCVP toxicity endpoints and points of departure (PODs) selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: For TCVP, there is no consistent pattern across studies, durations, lifestages, and routes. Following acute oral exposure, RBC and brain are equally affected, whereas the RBC compartment provided the lower BMDL estimate following repeat oral exposure in adults. Also, for each age group in the CCA studies, the magnitude of the RBC and brain inhibition is similar. Based upon the robustness of the AChE data and dose-response across the dose selection in the acute dose CCA rat study (see Appendix B for BMD analysis results), the RBC AChE data from PND 11 and 21 male and female pups were selected as the endpoint for deriving the acute and steady state POD for risk assessment.
- *Potentially susceptible populations (fetuses, juveniles, pregnant dams)*: The available AChE data across multiple lifestages (adults, pregnant females, fetuses, juveniles) show no quantitative sensitivity following repeat or acute exposure. The fetus is not more sensitive than the pregnant dam, and pregnant females were not more sensitive than non-pregnant females. There is also no consistent pattern with respect to sex difference. In the acute CCA, the adult male shows greater inhibition in both compartments than the adult female, whereas the adult female shows more inhibition (both compartments) in the repeat CCA and other repeat dose studies than the adult male.
- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with the exposure scenario(s) of interest. In the case of TCVP, there are single and repeat dose oral, repeat dose dermal, and repeat dose inhalation studies that contain measurements of RBC and brain AChE inhibition.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with the exposure duration of interest. In the case of TCVP, there are single day and steady state/repeat exposure oral studies and steady state dermal and inhalation studies. The oral AChE data show the magnitude of AChE inhibition does not significantly increase with time such that AChE inhibition from a single oral exposure is comparable to AChE inhibition after repeated oral exposure.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across



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studies. Based on a weight of evidence approach, the TCVP database allows for PODs to be derived from the most conservative BMDLs, which are consistent for the PND 11 and PND 21 rats in the acute CCA and adult animals in the acute and repeat CCA thereby increasing the confidence in such values.

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated $BMD_{10}$s and $BMDL_{10}$s. The $BMD_{10}$ is the estimated dose where AChE is inhibited by 10% compared to background AChE activity. The $BMDL_{10}$ is the lower confidence bound on the $BMD_{10}$ value. As a matter of science policy, the agency uses the BMDL, not the BMD, as the PoD (USEPA, 2012). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.4; an exponential model was used to fit the data. Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix A of this document, which includes an additional acute CCA identified since the last risk assessment. Summary tables of BMD analyses can be found in Appendix B and the technical details of the analysis can be found in the BMD memo (J. Bever; TXR No. 0056970; D420286).

*Acute Dietary (All Populations)*

A POD for the acute dietary (all populations) exposure scenario was derived from the results of the high quality, well-conducted acute dose CCA study (MRID 448773401a) in juvenile rats. Numerous estimates informed the $BMDL_{10}$ of 2.8 mg/kg/day, which was associated with RBC AChE inhibition in PND11 and PND 21 male and female juvenile rats and was therefore selected as the POD for the acute dietary exposure scenario for all populations. The lowest corresponding $BMD_{10}$ was 3.2 mg/kg/day. Data from the young rat from the acute CCA study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations.

The FQPA SF (10X) will be retained for infants, children, youths, and women of childbearing age due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5). The acute population adjusted dose (aPAD) for these lifestages is 0.0028 mg/kg/day (includes a total uncertainty factor of 1000X: 10X to account for interspecies extrapolation and 10X for intraspecies variation and the 10X FQPA SF). The only population subgroup for dietary exposure scenarios for which the FQPA SF is not retained is adults 50-99 years of age; therefore, the aPAD for this population subgroup is 0.028 mg/kg/day.

*Steady-State Dietary (All Populations)*

A POD for the steady-state dietary (all populations) exposure scenarios was derived from the same acute dose CCA study used for the acute dietary. A $BMDL_{10}$ of 2.8 mg/kg/day associated with RBC cholinesterase inhibition in male and female PND 11 and 21 rats was selected as a suitable POD for the steady-state dietary exposure scenario. The lowest corresponding $BMD_{10}$ was 3.2 mg/kg/day. Although the steady state dietary endpoint was selected from an acute dose comparative cholinesterase study, the duration of this study is considered appropriate for this exposure scenario since AChE data across the TCVP database demonstrate that there is no

progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose. A longer-term exposure does not result in a lower POD, as evidenced by the larger $BMD_{10}$s found for the repeat dose CCA data.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) is applied to the $BMDL_{10}$ to obtain an ssPAD of 0.0028 mg/kg/day for exposure scenarios with infants, children, youth, and women of child-bearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the ssPAD for this population subgroup is 0.028 mg/kg/day.

*Incidental Oral, Steady State*

For the purpose of assessing potential risk associated with incidental oral exposure from steady state durations, OPP selected the same POD (2.8 mg/kg/day) and endpoint as selected above for dietary exposure.

A total uncertainty factor of 1000X is appropriate for incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)). The Level of Concern (LOC) for incidental oral exposures is 1000.

*Dermal, Steady State*

No quantification of dermal non-cancer risk is required for TCVP since there were: (1) no treatment related effects (no clinical signs) at doses up to and including the limit dose of 1000 mg/kg/day in the dermal toxicity study; (2) both RBC and brain cholinesterase activity were assessed in the dermal study and neither compartment was affected at the limit dose; (3) there is no concern for quantitative susceptibility for juvenile or gestational lifestages based on results of the developmental, reproductive, or CCA toxicity studies.

*Inhalation, Steady State*

The steady state inhalation POD was selected from a 4-week inhalation toxicity study (MRID 48803501) in rats, based on an increase in RBC cholinesterase inhibition in both sexes. Females had slightly higher modeled values ($BMDL_{10}$ of 0.022 mg/L/day: $BMD_{10}$ of 0.12 mg/L/day) than males. The duration of this study is considered appropriate for the steady state exposure scenario since steady state occurs within 21 days, as demonstrated for other OPs, and a longer-term exposure would not be expected to result in a lower POD. The methods and dosimetry equations described in the agency's reference concentration (RfC) guidance are suited for calculating human equivalent concentrations (HECs) based on the inhalation toxicity POD obtained in rats exposed for 6 hours/day for an average of 5.5 days/week. The regional deposited dose ratio (RDDR), which accounts for the particulate diameter (mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD] of aerosols) can be used to estimate the different dose fractions deposited along the respiratory tract surface areas. Thus, the RDDR can

be used to adjust an observed inhalation particulate exposure of an animal to the predicted inhalation exposure for a human. For the subchronic inhalation toxicity study with TCVP, an RDDR of 2.525 was estimated based on extrarespiratory effects (RBC cholinesterase inhibition) in Sprague Dawley rats (bodyweight = 267g). The MMAD and GSD of 2.57 and 3.785 µm, respectively, at 0.05 mg/L were used to derive the RDDR.

The HECs are summarized in Table 4.6.4.3, as well as human equivalent doses (HEDs) calculated for residential and occupational handler scenarios. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

A total uncertainty factor of 300X is appropriate for inhalation exposures (3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments or a 10X database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)).

### 4.6.2 Recommendations for Combining Routes of Exposure for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major routes (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the oral, dermal, and inhalation routes are all derived from RBC cholinesterase inhibition. Thus, all routes can be combined.

### 4.6.3 Cancer Classification and Risk Assessment Recommendation

TCVP is classified as a Group C, possible human carcinogen, based on statistically significant increases in combined hepatocellular adenoma/carcinoma (primarily carcinomas) in the female B6C3F1 mouse, suggestive evidence of thyroid c-cell adenomas, and adrenal pheochromocytomas in the rat, as well as mutagenicity concerns. Following a reassessment of the mutagenicity data available on TCVP, it was determined that the relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[12]. A cancer potency factor ($Q_1{}^*$) of $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$ was estimated using the Weibull 83 time-to-tumor model. A 3/4 body weight scaling factor was used to convert from mouse to human equivalents. Following the submission and review of the required assays, the need for an updated cancer assessment will be determined.

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[12] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

### 4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

See Tables 4.6.4.1, 4.6.4.2, and 4.6.4.3 below.



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| Table 4.6.4.1. Summary of Toxicological Doses and Endpoints for TCVP for Use in Dietary and Non-Occupational Human Health Risk Assessments | | | | |
|---|---|---|---|---|
| **Exposure/ Scenario** | **Point of Departure** | **Uncertainty Factors*** | **Level of Concern for Risk Assessment** | **Study and Toxicological Effects** |
| Acute Dietary (all populations, except adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Acute RfD = 0.028 mg/kg/day<br>aPAD = 0.0028 mg/kg/day | Acute dose CCA study (MRID 48773401a) – Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND11 and 21 male and female RBC AChE inhibition |
| Acute Dietary (Adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 1x | Acute RfD = 0.028 mg/kg/day<br>aPAD = 0.028 mg/kg/day | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Steady State Dietary (all populations, except adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Steady State RfD = 0.028 mg/kg/day<br>ssPAD = 0.0028 mg/kg/day | Acute dose CCA study (MRID 48773401a) – Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Steady State Dietary (Adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 1x | Steady State RfD = 0.028 mg/kg/day<br>ssPAD = 0.028 mg/kg/day | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Incidental Oral (steady state) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Residential LOC for MOE = 1000 | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Dermal (steady state) | No potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day and no concern for quantitative susceptibility. | | | |

| | | | | |
|---|---|---|---|---|
| Inhalation (steady state) | $BMDL_{10}$=0.022 mg/L/day (males) | $UF_A$= 3x<br>$UF_H$=10x<br>FQPA SF = 10X | Residential LOC for MOE = 300 | Subchronic Inhalation Toxicity Study (MRID 48803501) – Rat<br><br>$BMD_{10}$ = 0.12 mg/L/day, based on RBC AChE inhibition in both sexes |
| Cancer (oral, dermal, inhalation) | Classification: A possible human (Group C) carcinogen. $Q_1$* = 1.83 x $10^{-3}$ (mg/kg/day)$^{-1}$ | | | |

[1] **Explanation of Abbreviations:** Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies); MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. AChE = acetylcholinesterase. $BMDL_{10}$= benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute. ss = steady state or maximal AChE inhibition.

*The 10X FQPA SF is retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 for which the FQPA SF has been reduced to 1X.

**Table 4.6.4.2 Summary of Toxicological Doses and Endpoints for TCVP for Use in Occupational Human Health Risk Assessments**

| Exposure/ Scenario | Point of Departure | Uncertainty Factors | Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Dermal (steady state) | No potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day and no concern for quantitative susceptibility. | | | |
| Inhalation (steady state) | $BMDL_{10}$=0.022 mg/L/day (males) | $UF_A$= 3x<br>$UF_H$=10x<br>$UF_{DB}$= 10x[A] | Occupational LOC for MOE = 300 | Subchronic Inhalation Toxicity Study (MRID 48803501) - Rat<br><br>$BMD_{10}$ = 0.12 mg/L/day, based on RBC AChE inhibition in both sexes |
| Cancer (oral, dermal, inhalation) | Classification: A possible human (Group C) carcinogen. $Q_1$* = 1.83 x $10^{-3}$ (mg/kg/day)$^{-1}$ | | | |

[1] **Explanation of Abbreviations:** Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UFA = extrapolation from animal to human (interspecies). UFH = potential variation in sensitivity among members of the human population (intraspecies); $UF_{DB}$ = database uncertainty factor; MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$= benchmark dose lower limit for 10% response. AChE = acetylcholinesterase. SS = steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted

for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations including chronic.
[A] The 10X database uncertainty factor applies to occupational worker assessment to account for potentially pregnant workers due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

**Table 4.6.4.3 Summary of HEC/HED Values for TCVP**

| Population | Scenario | Tox Duration Adjustment | | HEC | | HED |
|---|---|---|---|---|---|---|
| | | hours/day[a] | days/week[b] | mg/L | mg/m³ | mg/kg/day |
| Occupational | Handler | 0.75 | 1 | 0.042 | 41.663 | 3.94 |
| Residential | Handler | | | 0.056 | 55.550 | 1.31 |
| | Bystander | 0.25 | 0.714 | 0.010 | 9.920 | |

HEC = human-equivalent concentration; HED = human-equivalent dose. See Appendix C for details.
HEC = rat POD × daily duration adjustment × weekly daily duration adjustment × RDDR.
HED = HEC × human-specific conversion factor (11.8 L/hr/kg) × daily duration.
[a] hours of exposure [animal study (6 hours) ÷ human worker (8 hours) or bystander (24 hours)]
[b] days of exposure [animal study (5 days/week ÷ bystander (7 days/week)/human worker (5 days/week)]

## 4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for TCVP, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), TCVP is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[13] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. TCVP is on List 1 for which EPA has received all the required Tier 1 assay data. The agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[14].

## 5.0 Dietary Exposure and Risk Assessment

### 5.1 Metabolite/Degradate Residue Profile

#### 5.1.1 Summary of Plant and Animal Metabolism Studies

Residue Chemistry Memo: DP# 243528, 3/11/98, D. Miller
Residue Chemistry Memo: DP# 206721, 9/21/94, D. Miller (Addendum to RED)
Residue Chemistry Chapter to Tetrachlorvinphos RED (DP# 199644, 7/6/94, F. Suhre)
Residue Chemistry Memo: J. Abbotts, No DP#, 4/93, Results of Metabolism Committee Meeting

There are no registrations or tolerances for plant commodities, so plant metabolism studies are not required for TCVP. The qualitative nature of the residue in ruminants following oral or dermal dosing, and in poultry following dermal application, is adequately understood based on previously submitted studies. The HED Metabolism Committee (9/8/93 Meeting) has determined that the residues of concern for tolerance enforcement and for risk assessment for carcinogenicity are the parent compound and four metabolites: tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. For the non-cancer risk assessment for cholinesterase inhibition, tetrachlorvinphos is the only residue of concern.

#### 5.1.2 Summary of Environmental Degradation

Drinking Water Assessment Memo (EFED): DP# 419448, 11/6/14, C. Peck[15]

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[13] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of
chemicals.
[14] http://www.epa.gov/endo/
[15] C. Peck, 11/6/2014, D419448, Tetrachlorvinphos (TCVP) Drinking Water Assessment for Registration Review



ED_002155B_00027950-00040

TCVP is moderately mobile in soil and not stable in terrestrial or aquatic environments. The TCVP degradates appear to be as mobile, and in most cases more mobile, than the parent. TCVP is soluble in water at up to 11.6 mg/L, and is not expected to volatilize significantly due to a low vapor pressure of 2.6 x $10^{-7}$ torr (25°C). The compound is hydrophobic (Log $K_{ow}$ of 3.53). TCVP hydrolyzes in water at a pH-dependent rate. Hydrolysis is relatively rapid in alkaline water (half-life of 10.3 days at pH 9). In neutral to acidic water (pH 5 to 7), TCVP hydrolyzes with slower half-lives of 30 to 57 days. A major degradate of hydrolysis found in the aqueous solution at pH 9 was des-O-methyl tetrachlorvinphos (28% at Day 21). Hydrolysis rates for the TCVP Total Residue of Concern (TRC) could not be calculated, as not all degradates in the study extracts were identified; therefore, TCVP TRC was considered stable to hydrolysis.

TCVP isomer mixture (50:50, Z:E) readily biodegraded in aerobic soils, with a half-life of approximately 9 days. However, the rate of biodegradation for the mixed isomer of the parent TCVP was slightly reduced as concentrations decreased, which may indicate that one isomer degrades more rapidly than the other. Major soil degradates include TCPEol, TCCEol, TCPEone and TCBA. The TCVP TRC that were identified in the aerobic soils biodegraded with half-lives of from 53 to 200 days.

### 5.1.3 Comparison of Metabolic Pathways

Metabolism in ruminants (dermal and oral administration; tissue), poultry (oral; tissue) and rats (oral; excreta) is similar, generally resulting in parent TCVP and the four metabolites of concern (TCVPdeme, TCPEdiol, TCPEone and TCPEol). However, the metabolite TCPEone was not found in detectable levels in the rat metabolism study and the metabolite TCPEdiol was not detected in the goat studies. Unchanged parent TCVP was found in the goat dermal study, but was not detected in the goat oral study.

### 5.1.4 Residues of Concern Summary and Rationale

The HED Metabolism Committee (9/8/93 Meeting) has determined that the total residues of concern (TRC) for carcinogenicity are the parent compound tetrachlorvinphos and metabolites which, like tetrachlorvinphos, contain the 2,4,5 trichlorobenzene ring. For livestock commodities, the total residues of concern for carcinogenicity are tetrachlorvinphos [TCVP] plus the following four metabolites: des-O-methyl tetrachlorvinphos [TCVPdeme]; 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms) [TCPEol]; 2,4,5-trichloroacetophenone [TCPEone]; and 1-(2,4,5-trichlorophenyl)ethanediol [TCPEdiol]. For drinking water carcinogenicity assessment, the total residues of concern include the four aforementioned metabolites for livestock plus 2 additional degradates: 1-(2,4,5-trichlorophenyl)-2-chloroethanol [TCCEol], and 2,4,5-trichlorobenzoic acid [TCBA].

For the non-cancer risk assessment for cholinesterase inhibition, TCVP is the only residue of concern. For tolerance enforcement the residues of concern include TCVP plus, TCVPdeme, TCPEdiol, TCPEone and TCPEol.

See Appendix E for a table of parent and metabolite structures and chemical properties.

| Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression | | | | |
|---|---|---|---|---|
| **Matrix** | | **Residues included in Risk Assessment (Cholinesterase Inhibition)** | **Residues included in Risk Assessment (Carcinogenicity)** | **Residues included in Tolerance Expression** |
| Plants | Primary Crop | NA | NA | NA |
| | Rotational Crop | NA | NA | NA |
| Livestock | Ruminant | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol |
| | Poultry | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol |
| Drinking Water | | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol, TCCEol, TCBA | NA |

NA= not applicable
TCVP= tetrachlorvinphos
TCVPdeme,= des-O-methyl tetrachlorvinphos
TCPEol= 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms)
TCPEone= 2,4,5-trichloroacetophenone
TCPEdiol= 1-(2,4,5-trichlorophenyl)ethanediol
TCCEol =l-(2,4,5-trichlorophenyl)-2-chloroethanol
TCBA =2,4,5-Trichlorobenzoic acid

## 5.2 Residue Chemistry and Food Residue Profile

Residue Chemistry Memo: D243528, 3/11/98, D. Miller

*Residue Chemistry*

Tolerances are established for residues of TCVP in animal commodities since residues may occur in milk, eggs, meat, fat, or meat byproducts as a result of the registered uses on livestock (oral and dermal uses) and around livestock premises. There are no registered uses on plant (including feedstuffs) commodities. This section provides the background and current status of residue chemistry requirements for TCVP and includes residue data submitted and reviewed since the 1994 Residue Chemistry Chapter of the TCVP RED and the 2006 TCVP RED.

The 1994 Residue Chemistry Chapter cited the need for the following magnitude of the residue studies: *New magnitude of the residue studies reflecting oral and dermal exposure of beef cattle, dairy cattle, and hogs, and dermal exposure of poultry to tetrachlorvinphos are required. All residues of concern should be analyzed in cattle, hogs, and poultry using validated analytical methods.*

Subsequent to the TCVP RED, in 2007, residue studies on cattle (dermal and oral treatments; MRID 47193001) and poultry (dermal treatment; MRID 47193001) were submitted, as was a companion storage stability study (MRID 47193001) and a residue analytical method (MRID 47369201). Those studies were reviewed under DP #s D320848, D320858, D320859, and D381350 (C. Olinger, 10/7/10, *Tetrachlorvinphos. Cattle Oral/Dermal and Poultry Dermal Studies. Summary of Residue Data Submitted in Support of Reregistration*). The submitted magnitude of the residue studies on cattle and poultry were determined to be inadequate, but upgradeable pending submission of supporting storage stability data. The companion storage stability study was determined to be unacceptable because of study design. Additional information was also requested regarding the maximum storage duration of all samples collected from both the cattle and poultry studies. In 2011, additional information (MRIDs 486378101 and 48319001) pertaining to the storage stability deficiencies was submitted and reviewed (C. Olinger, 3/25/11, D385359 and D386954, *Tetrachlorvinphos. Response to Comment on Storage Stability Residue Data Deficiencies)*. The poultry and cattle residue data (860.1480) deficiencies are now fulfilled and no further data are being required.

In response to the data requirement for a residue study in hogs, a waiver request was submitted and granted in 2011 (C. Olinger, 4/25/11, D320857, *Tetrachlorvinphos. Request for Waiver of a Swine Magnitude of Residue Study).* It was determined that TCVP residues in swine tissues are not likely to be higher than the residues in ruminants and that ruminant data may be translated to swine. The conclusion was based on the poor oral and dermal absorption of TCVP in livestock and the fact that residence time in swine intestines is significantly shorter relative to that in a ruminant. No additional residue data (860.1480) on hogs are being required.

In response to a TCVP Generic Data Call-In (GDCI) issued 12/29/09, data were submitted evaluating TCVP metabolites using the FDA Multiresidue Methods Test guidelines in Pesticide Analytical Manual (PAM) Vol. I (MRID 48655201) and were reviewed 7/5/12 (D. Drew, D396833, *Tetrachlorvinphos (TCVP). Multiresidue Methods (MRM) Study of the Metabolites of TCVP*). The data requirement for MRM testing (860.1360) has been fulfilled.

The registrant submitted a proposed method SCR/006 for tolerance enforcement of livestock commodities that includes detection of TCVP and the metabolites TCVPdeme, TCPEol, TCPEone and TCPEdiol (MRID 47369201, 2007). The HED review (D320848, D320858, D320859, and D381350) determined that the method was adequate, but that an independent laboratory validation (ILV) trial remained outstanding. A Generic Data Call-In (GDCI) for an ILV was originally issued December 29, 2009. A different proposed method (Method 14020.6106) and an associated ILV study (Method 14020.6107) were subsequently submitted to the agency (MRID 49419301, 2015). Because the proposed Method 14020.6106 monitors only a single ion transition for each analyte, alternative confirmatory procedures are necessary; the previously submitted method SCR/006 (MRID 47369201) is considered acceptable as a confirmatory method. The analytical method test data for 14020.6106 are classified as scientifically acceptable for use as an analytical method for ruminant and poultry commodities.

*Food Residue Profile*

The available magnitude of the residue study for dairy cattle reflect a combination of two treatments: oral administration of tetrachlorvinphos for 29-31 days at actual rates of 1.51-1.55 and 4.63 g ai/750 kg BW per day (6.3-6.5x and 19.3x, respectively, the maximum registered rate of 0.24 g ai/750 kg BW for feed-through treatment) and dermal spray treatments on three occasions, at ~14 day intervals, at actual rates of 10.11 and 19.2-19.5 g ai per animal per dose (~0.5 and 1.0x, respectively, the maximum registered rate of 18.9 g ai/animal for direct animal spray treatment). At the combined treatment regime (6.5x dermal spray plus 1x oral treatment), the maximum total residues of concern (with the maximum residues of the parent in parentheses) were: 0.072 (0.036) ppm for milk, 0.078 (<0.01) ppm for cream, 0.158 (<0.01) ppm for liver, 0.278 (0.015) ppm for kidney, 0.272 (0.212) ppm for muscle, 0.842 (0.558) ppm for subcutaneous fat, and 0.747 (0.340) ppm for peritoneal fat.

The available magnitude of the residue study for poultry reflects 6-7 dermal spray treatments of laying hens with an EC formulation, made at two-week retreatment intervals, at 0.0908, 0.182, or 0.545 g ai/hen/application. These application rates, respectively, correspond to ~0.5x, 1.0x, or 2.9x the maximum registered direct spray treatment rate of 0.19 g ai/bird daily. At ~1.0x, the maximum total residues of concern (with the maximum residues of the parent in parentheses) were: 0.288 (0.026) ppm for egg, 0.517 (0.016) ppm for liver, 0.583 (0.022) ppm for kidney, 0.396 (0.082) ppm for muscle, 19.405 (6.030) ppm for skin with fat, and 1.298 (0.099) ppm for abdominal fat.

There were no detectable residues of parent TCVP in the most recent USDA PDP monitoring data for beef meat, liver, or fat, or for milk and cream; nor were there detectable residues in pork fat. There were no detectable residues in chicken meat or liver. There was one detectable residue in egg just above the method limit of detection (LOD; 742 samples). PDP did not analyze chicken fat or skin for TCVP. The TCVP metabolites of concern for cancer assessment were not measured by PDP.

## 5.3 Water Residue Profile

Drinking Water Assessment Memo (EFED): D419448, 11/6/14, C. Peck

The Surface Water Concentration Calculator (SWCC) computer model was used to generate surface water Estimated Drinking Water Concentrations (EDWCs) for use in the human health dietary risk assessment, while the PRZM-GW and SCI-GROW models were used to generate groundwater EDWCs. The residues of concern for acute and steady state dietary exposure included cholinesterase-inhibiting compounds, which were determined to be TCVP parent only. For carcinogenicity, (total) residues of concern (TRC) included TCVP and the following metabolites which, like TCVP, contain the 2,4,5 trichlorobenzene ring: des-O-methyl tetrachlorvinphos,1-(2,4,5-trichlorophenyl)ethanediol, TCPEol (1-(2,4,5-trichlorophenyl)ethanol), TCPEone (2,4,5-trichloroacetophenone), TCCEol (l-(2,4,5-trichlorophenyl)-2-chloroethanol), and TCBA (2,4,5-trichlorobenzoic acid).

Maximum EDWCs (based on maximum labeled usage for kennels, poultry droppings, garbage and manure piles, and corrals) for TCVP residues in surface water and groundwater for dietary assessment are presented in Table 5.3. Daily time series outputs for the thirty year simulation were also provided to HED for use in dietary exposure modeling.

This dietary assessment used the maximum total residues of concern (TRC) EDWC of 22.4 ug/L for the cancer analysis, input as a single point estimate. For the selected drinking water scenarios, a distribution of surface water residues was used probabilistically in the dietary model for non-cancer assessments based on cholinesterase inhibition. The following paragraph describes the derivation of those distributions.

Daily time-series outputs that simulate 29 years (1962-1990) of residues of TCVP in surface drinking water for the outdoor uses (on kennels, poultry droppings, garbage and manure piles, and corrals) were modeled using the SWCC. No further adjustments were made to the acute distribution files, but since the steady state average dietary assessments use 21-day forward rolling averages for drinking water, the steady state distributions were further adjusted to be 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc. The 21-day rolling average continues until the last 20 days of residues of the final distribution year.

**Table 5.3 Summary of Estimated Surface Water and Groundwater Concentrations for Tetrachlorvinphos**

| DRINKING WATER SOURCE (MODEL USED) | MAXIMUM ESTIMATED DRINKING WATER CONCENTRATION (EDWC) | |
|---|---|---|
| | Acute (µg/L) (TCVP only) | Cancer (µg/L) (TRC) |
| Surface water (SWCC) | **4.03** | 4.11 |
| Groundwater (PRZM-GW) | $8.54 \times 10^{-5}$ | **22.4** |
| Groundwater (SCI-GROW) | $5.61 \times 10^{-3}$ | $7.36 \times 10^{-2}$ |

* EDWCs based on maximum labeled usage for kennels, poultry droppings, garbage and manure piles, and corrals.

## 5.4 Dietary Risk Assessment

Dietary Assessment Memo: D436835, 9/20/2016, D. Drew[16]

[16] D. Drew, 9/20/2016, Tetrachlorvinphos (TCVP). Revised Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment, D436835.

The previous dietary risk assessment for tetrachlorvinphos was conducted on 10/29/2014 (D. Drew, D426985, *Tetrachlorvinphos (TCVP) Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment*). That assessment has been updated in D436835 (D. Drew, 9/20/2016, Tetrachlorvinphos (TCVP). *Revised Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment*) to reflect changes in the toxicological PODs for the acute and steady state dietary exposures. In addition, minor corrections have been made based on comments received on the 2014 dietary assessment (MRID 4989101, Bayer CropScience, *Comments to EPA's "Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment for Registration Review", Docket ID: EPA-HQ-OPP-2008-0316*).

### 5.4.1 Description of Residue Data Used in Dietary Assessment

HED has conducted acute, steady state, and cancer dietary (food and drinking water) exposure and risk assessments using DEEM version 3.16 for TCVP.

The dietary exposure analyses for TCVP are refined. The only food forms included in the analyses are based on animal commodities. The food residues were based upon U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) monitoring data except in a couple of instances where no appropriate PDP data were available (i.e., high-end residues from poultry dermal studies were used for poultry fat and poultry skin). The Biological and Economic Analysis Division (BEAD) of OPP provided percent livestock treated information. Model-derived estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effect Division (EFED). EDWCs were based on spot applications to kennels, poultry droppings, garbage and manure piles, and corrals and were directly incorporated into the assessments as described in Section 5.3 above.

Since the PDP only analyzed for residues of TCVP (and not for TCVP metabolites) a factor was applied to the PDP residues in order to account for all the metabolites of concern for the cancer assessment. The factor was calculated by determining the ratio of parent TCVP to total residues of concern in the livestock residue studies (see Table 2, D436835).

### 5.4.2 Percent Crop Treated Used in Dietary Assessment

For the acute and steady state analyses, the maximum estimated percent livestock treated of 3% was used for cattle and swine and the estimated maximum of 11% was used for poultry.

For the cancer analysis, the following estimated average percent livestock treated values were used: 1% for dairy cattle, 2% for beef cattle and swine, and 6% for poultry.

### 5.4.3 Acute Dietary Risk Assessment

The refined acute dietary (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 190% of the aPAD.

When drinking water is analyzed by itself, the acute dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95th and 99.9th percentile of exposure.

Most of the exposure from food is due to the high-end residue on chicken skin from poultry dermal studies (residue on uncooked chicken skin from direct dermal spray applications at maximum labeled rates with a 0-day pre-slaughter interval).

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

**Table 5.4.3.1. Results of Acute Dietary (Food Only) Exposure and Risk Analysis.**

| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.0028 | 0.000022 | < 1 | 0.000680 | 24 | 0.002806 | 100 |
| All Infants (<1 year old) | 0.0028 | 0.000012 | < 1 | 0.000288 | 10 | 0.002739 | 98 |
| Children 1-2 years old | 0.0028 | 0.000069 | 2.5 | 0.001073 | 38 | 0.004708 | 170 |
| **Children 3-5 years old** | 0.0028 | 0.000054 | 1.9 | 0.001386 | 50 | 0.005230 | 190 |
| Children 6-12 years old | 0.0028 | 0.000037 | 1.3 | 0.000938 | 33 | 0.003941 | 140 |
| Youth 13-19 years old | 0.0028 | 0.000024 | < 1 | 0.000731 | 26 | 0.003318 | 120 |
| Adults 20-49 years old | 0.0028 | 0.000022 | < 1 | 0.000722 | 26 | 0.002584 | 92 |
| Adults 50-99 years old | 0.028 | 0.000011 | < 1 | 0.000492 | 1.8 | 0.001690 | 6.0 |
| Females 13-49 years old | 0.0028 | 0.000020 | < 1 | 0.000651 | 23 | 0.002300 | 82 |

[1] Population with the greatest exposure is in bold.
[2] aPAD = acute population-adjusted dose.

**Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only) Exposure and Risk Analysis.**

| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000121 | 4.3 |
| **All Infants (<1 year old)** | 0.0028 | 0.000022 | < 1 | 0.000093 | 3.3 | 0.000369 | 13 |
| Children 1-2 years old | 0.0028 | 0.000012 | < 1 | 0.000048 | 1.7 | 0.000187 | 6.7 |

| Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| Children 3-5 years old | 0.0028 | 0.000011 | < 1 | 0.000041 | 1.4 | 0.000147 | 5.2 |
| Children 6-12 years old | 0.0028 | 0.000008 | < 1 | 0.000030 | 1.1 | 0.000111 | 4.0 |
| Youth 13-19 years old | 0.0028 | 0.000006 | < 1 | 0.000025 | < 1 | 0.000095 | 3.4 |
| Adults 20-49 years old | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000118 | 4.2 |
| Adults 50-99 years old | 0.028 | 0.000009 | < 1 | 0.000032 | < 1 | 0.000110 | < 1 |
| Females 13-49 years old | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000120 | 4.3 |

[1] Population with the greatest exposure is in bold.
[2] aPAD = acute population-adjusted dose.

### 5.4.4 Steady State Dietary Risk Assessment

The refined steady state (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the steady state population adjusted dose (ssPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 120% of the ssPAD.

The steady state dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95th and 99.9th percentile of exposure.

Most of the exposure from food is due to the high-end residue on chicken skin from poultry dermal studies (residue on uncooked chicken skin from direct dermal spray applications at maximum labeled rates with a 0-day pre-slaughter interval).

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

| Table 5.4.4.1. Results of Steady State Dietary (Food Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| General U.S. Population | 0.0028 | 0.000092 | 3.3 | 0.000599 | 21 | 0.001994 | 71 |
| All Infants (<1 year old) | 0.0028 | 0.000020 | < 1 | 0.000299 | 11 | 0.001843 | 66 |
| Children 1-2 years old | 0.0028 | 0.000128 | 4.6 | 0.001070 | 38 | 0.003181 | 110 |
| **Children 3-5 years old** | 0.0028 | 0.000152 | 5.4 | 0.001214 | **43** | **0.003444** | **120** |
| Children 6-12 years old | 0.0028 | 0.000130 | 4.6 | 0.000782 | 28 | 0.002991 | 110 |
| Youth 13-19 years old | 0.0028 | 0.000116 | 4.1 | 0.000645 | 23 | 0.002118 | 76 |
| Adults 20-49 years old | 0.0028 | 0.000112 | 4.0 | 0.000621 | 22 | 0.001971 | 70 |

| Table 5.4.4.1. Results of Steady State Dietary (Food Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| Adults 50-99 years old | 0.028 | 0.000049 | < 1 | 0.000418 | 1.5 | 0.001105 | 3.9 |
| Females 13-49 years old | 0.0028 | 0.000098 | 3.5 | 0.000572 | 20 | 0.001481 | 53 |

[1] Population with the greatest exposure is in bold.
[2] ssPAD = steady state population-adjusted dose.

| Table 5.4.4.2. Results of Steady State Dietary (Drinking Water Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| General U.S. Population | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000096 | 3.4 |
| **All Infants (<1 year old)** | 0.0028 | 0.000024 | < 1 | 0.000088 | 3.2 | 0.000300 | 11 |
| Children 1-2 years old | 0.0028 | 0.000013 | < 1 | 0.000045 | 1.6 | 0.000143 | 5.1 |
| Children 3-5 years old | 0.0028 | 0.000011 | < 1 | 0.000038 | 1.4 | 0.000114 | 4.1 |
| Children 6-12 years old | 0.0028 | 0.000008 | < 1 | 0.000028 | < 1 | 0.000085 | 3.0 |
| Youth 13-19 years old | 0.0028 | 0.000007 | < 1 | 0.000023 | < 1 | 0.000075 | 2.7 |
| Adults 20-49 years old | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000094 | 3.4 |
| Adults 50-99 years old | 0.028 | 0.000009 | < 1 | 0.000030 | < 1 | 0.000087 | < 1 |
| Females 13-49 years old | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000095 | 3.4 |

[1] Population with the greatest exposure is in bold.
[2] ssPAD = steady state population-adjusted dose.

### 5.4.5 Cancer Dietary Risk Assessment

The refined cancer dietary (food and drinking water) assessment resulted in an estimated exposure to TCVP and its metabolites containing the 2,4,5 trichlorobenzene moiety (the residues of concern for cancer) of 0.000513 mg/kg/day. Applying the $Q_1$* of 0.00183 $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of $9 \times 10^{-7}$. Drinking water is the major contributor to the cancer dietary risk estimate.

| Table 5.4.5.1. Summary of CANCER Dietary Exposure and Risk for Tetrachlorvinphos (and metabolites). | | | | | | |
|---|---|---|---|---|---|---|
| Population Subgroup | Food and Water | | Food Only | | Water Only | |
| | Exposure (mg/kg/day) | Risk | Exposure (mg/kg/day) | Risk | Exposure (mg/kg/day) | Risk |
| Adults | 0.000513 | $9 \times 10^{-7}$ | 0.000044 | $8 \times 10^{-8}$ | 0.000469 | $8 \times 10^{-7}$ |

## 6.0 Residential and Non-Occupational Exposure/Risk Characterization

Occupational and Residential Exposure Memo: D436833, 12/21/2016, W. Britton [17]

Residential exposures (handler and post-application) are anticipated from the use of TCVP pet products for dogs and cats including collars, dusts/powders, and pump/trigger sprays. Exposures are expected for adults who apply TCVP products to their pets and from post-application exposures for adults and children who may contact previously treated pets. Residential TCVP handler and post-application exposures are anticipated to be short- (1 to 30 days), intermediate- (1 to 6 months), and long-term (>6 months – *for pet collar scenarios only*). However, because of the steady state AChE inhibition exhibited by the OPs, steady state (typically 21 days and longer for OPs, but 1 day for TCVP) residential exposures were assessed for TCVP pet products.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

Following EPA's December 21, 2015 Draft TCVP risk assessment, Bayer HealthCare, Hartz Mountain Corporation, and NRDC submitted comments during the public comment period, primarily regarding the formulation type of pet collars. This document addresses, where appropriate, those comments. A comprehensive response to comments on the TCVP draft human health risk assessment (including ORE-specific comments) is also provided in the following memo: D. Drew et al., Tetrachlorvinphos (TCVP) Health Effects Division Response to Comments on the December 21, 2015 Draft Human Health Risk Assessment for TCVP Registration Review, D433403, 12/21/2016.

Formulation Type Issue: In 2009, the Natural Resources Defense Council (NRDC) petitioned the EPA to cancel all pet uses for the pesticide tetrachlorvinphos (TCVP). In 2014, the agency responded to the 2009 petition by conducting a human health risk assessment for all currently registered TCVP products which include collars, dusts/powders, and pump and trigger spray formulations. That risk assessment was dated Nov. 5, 2014. At that time, no human health risks of concern were identified for any TCVP pet product, and the petition to cancel all pet products was denied on Nov. 6, 2014. The NRDC subsequently responded to the agency's denial with arguments presented in NRDC's Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.) (Opening Brief). Among the arguments raised by NRDC was the assertion that the agency incorrectly considered the TCVP flea collar formulation to be a liquid formulated product:

*"NRDC states that the EPA failed to 'research' the TCVP flea collar label; instead it ignored the information in the label right on the box regarding the chemical formulation.' [NRDC Opening*

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[17] W. Britton *et al.*, 12/21/2016, D436833, Tetrachlorvinphos: Final Occupational and Residential Exposure Assessment for Registration Review

*Brief, p.67]. The label for the Hartz UltraGuard Flea and Tick Collar for Dogs (EPA Reg. No. 2596-84) states that 'as the collar begins to work, a fine white powder will appear on the surface.' As a result, NRDC argues that the transfer coefficient (TC) recommended for solid formulations should have been used instead of the transfer coefficent for liquid formulations as is recommended by the 2012 Residential SOPs."*[18]

The agency responded to this and all other arguments raised by NRDC in a December 21, 2015 memorandum,[19] issued along with the Draft risk assessment for Registration Review. The following is an excerpt of the agency's response relating to the pet collar formulation issue:

*"Per EPA's 2012 Residential SOPs*[20]*: Treated Pets, pet collar products are categorized as a liquid formulation. This position was based on research conducted at the time of SOP development that supported that pet collars function by means of diffusion, transferring from the collar to the surrounding area. More specifically, the active ingredient, which is embedded in the collar matrix, diffuses slowly through the matrix, thus controlling the amount of the active ingredient at the collar's surface. The active ingredient available on the surface of the pet collar then "rubs off" or transfers from the collar to the animal's hair coat via embedded lubricants which function as transfer agents at the surface of the collar. Based on the categorization of pet collars as liquid formulations, the assessment of post-application exposures for these product types would be conducted with use of the TCs, and the fraction active ingredient on the hands from TC studies ($Fai_{hands}$) recommended for the assessment of liquid formulated products as recommended in the 2012 Residential SOPs.*

*The information provided by NRDC states that the label for the Hartz UltraGuard Flea and Tick Collar for Dogs (EPA Reg. No. 2596-84) states that "as the collar begins to work, a fine white powder will appear on the surface." HED has confirmed that this statement is present on the current labeling for the identified product and that an identical statement is also found on the following TCVP pet collar products (5 of 9 total pet collar products): EPA Reg. Nos. 2596-62, 2596-63, 2596-83, 2596-84, and 2596-139. Taking label statements into account, and based upon further research which suggests that some pet collars may act by extrusion of the active ingredient from the collar matrix as a fine dust, HED has reconsidered the position that the TCVP pet collars are all liquid formulated products. As a result of this uncertainty, in the TCVP draft human health risk assessment in support of registration review, HED has updated the assessment of post-application risks from TCVP pet collars in consideration of both the dust- and liquid-specific TCs and $Fai_{hands}$ recommended SOP values."*[21]

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[18] W. Britton. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589, at 8 (summarizing NRDC's argument).

[19] *Id.*

[20] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[21] *Id.* at 8-9.

In response to the 2015 Draft TCVP risk assessment, Bayer HealthCare submitted comments to address the formulation type issue. Bayer agreed with the approach employed by the agency, stating: "*Based on the NRDC assertion and the statement on the collar packaging the agency has taken the understandable approach of calculating the post-application exposure, using both liquid and solid formulation transfer coefficients, until the uncertainty is resolved.*" Bayer proceeded to address the formulation type issue by describing how the active ingredient is released from the collar and distributed on the animal. Bayer described that, "*To achieve their goal of effective pest control, the flea collars are designed to deliver the insecticide from the collar in either a liquid or solid state. The collar is made from a mixture of plastic resins and resin modifiers. The resins are formulated to have appropriate strength and flexibility so the collar can withstand the shaping operations without cracking or crumbling. The resins must also have appropriate release characteristics, such that the TCVP (or other insecticide active ingredient) can escape the collar at the proper rate, while inert components remain in the collar.*"

Per Bayer, TCVP is distributed on the animal by abrasion or movement against the animal or diffusion from the animal's body heat. "*Within a few days after manufacture, the insecticide begins to migrate from within the body of the collar and form a coating of particles, resembling a dust or powder on the surface of the collar. As the particles of the active ingredient are displaced or shaken from the surface due to the normal activity of the animal, additional particles appear by migration from the body of the composition to replace the insecticide particles displaced from the surface (i.e., the displaced particles are replenished continuously). This describes the typical release mechanism and explains the presence of the powder as raised by NRDC. The powders are in the immediate vicinity of the collar; however, this is not necessarily the form in which the insecticide is dispersed to the animal or relevant to the transfer coefficient.*" They continued to describe that the sebaceous glands within the dog's skin that lubricate the hair are the mechanism for dispersion of the insecticide. "*Insecticides that are used in flea collars are lipophilic and soluble in the animal's skin oils. So, even though the collars may release some of the insecticides as a solid they are dispersed along the animal's body as a solution or suspension in the animal's skin via the natural skin oils.*" As such, the assessment of human health risks from TCVP pet collars were conducted in a manner that accounts for the likelihood of the presence of both liquid and solid forms while considering the isolated location (i.e., the head/neck) of ai in the dust/powder form.

While informative, Bayer's comments pose a dilemma for the agency. Although they describe the mechanism of dispersion of active ingredient along the animal's body as a solution or suspension in the skin, they also indicate that the insecticide begins to migrate from within the collar as a "coating of particles, resembling a dust or powder form on the surface of the collar" and that "flea collars are designed to deliver the insecticide from the collar in either a liquid or solid state." The mechanism of active ingredient dispersion via the skin alone is not adequate to describe the potential for post-application exposures. If the active ingredient is present as a liquid or particulate or dust on the surface of the pet collar, it could be transferred in either form from the collar to the pet's fur immediately surrounding and result in the potential for post-application exposures from either direct contact with the pet collar, or the surrounding fur.

Formulation Type Approach: A unique approach has been applied in order to account for the potential for exposures from the presence of TCVP to exist as both liquid and solid forms concurrently. The approach uses the same methodologies described in the 2012 Residential SOPs for assessment of residential handler and post-application exposure assessment for pet collar usage. However, whereas the 2012 Residential SOPs recommend that pet collars be assessed as a liquid formulation, the present approach assesses pet collar exposures as both a liquid and solid form. For residential handlers, this means use of the liquid UE data as recommended by the 2012 Residential SOPs and chemical-specific dust UE data for these formulation types. For the residential post-application exposure assessment, this means use of transfer coefficients (dermal exposures) and the fraction of active ingredient on hands from the transfer coefficent studies (hand-to-mouth exposures) specific to both liquid and solid formulation types.

The individual dust and liquid formulation handler and post-application doses were estimated, and then another step was included in the assessment where the liquid and dust doses were averaged assuming a ratio of liquid to dust in the collar formulation. For both handler and post-application scenarios, ratios of 1/99, 50/50, and 99/1 liquid/dust were assumed to cover a range of potential exposures.

The methodologies and inputs used for the individual formulation assessments for residential handlers and residential post-application exposures are described in Appendix B of the corresponding ORE memo (Memo, W. Britton *et al*, D436833).

Due to NRDC's argument related to the TCVP pet collar formulation, the agency has begun efforts to reevaluate pet collar formulation type to carefully consider whether pet collar products are more closely related to more traditional liquid formulation pet products such as shampoos and spot-ons, or solid formulated products such as dusts and powders. In following with this evaluation, the agency intends to request and review additional information relating to all registered pet collar products as they undergo registration review, as well as any proposed new pet collar uses. This evaluation will continue until the agency is satisfied that, based on the design and operation of pet collar products, a final formulation type decision can be made along with recommendations for human health risk assessment of exposures to pet collar-treated pets.

## 6.1 Residential Handler Exposures

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are assumed to complete all elements of an application without use of any protective equipment.

Residential handler exposures to TCVP pet products may occur via the dermal or inhalation routes while the product is placed on a cat or dog. Both steady state non-cancer and cancer residential handler exposure assessments were performed for adult homeowners applying TCVP pet collars, dusts/powders, and pump/trigger sprays products to cats and dogs. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are

assessed.

The exposure data and assumptions that underlie the residential handler non-cancer risk estimates can be referenced in the 2014 residential assessment[22] and the 2012 Residential SOPs. The algorithms used to estimate non-cancer exposure and dose for residential handlers can be found in Appendix B of the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833) and/or the 2012 Residential SOPs.[23]

Due to the uncertainty associated with whether TCVP pet collars are liquid and/or dust formulated products, residential handler steady state inhalation exposures for TCVP pet collar application were assessed (as described above in Section 6.0) assuming pet collars could be liquid and solid (dust) formulations concurrently, with varying ratios liquid/dust. When assuming the TCVP pet collars are a liquid formulation, the liquid-specific unit exposures (UE) values (i.e., surrogate data from a spot-on applicator study) from the 2012 Residential SOPs were used. When assuming the pet collars are a solid formulation, HED used the best available data, a TCVP dust/powder applicator exposure study (MRID 45519601).

The liquid formulation spot-on surrogate UE data assumes negligible inhalation exposure; therefore, only the dust-specific UE data (i.e., a TCVP dust/powder applicator exposure study) is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates

*Pet Collars:* Because there is uncertainty whether the TCVP pet collars are liquid and/or dust formulated products, residential handler (adults) steady state inhalation exposures were evaluated assuming both liquid and solid (dust) formulations are present concurrently with varying ratios of liquid/dust. No inhalation risks of concern were identified for residential handlers for any liquid/dust formulation ratio assumption. When assuming a ratio of 1/99 liquid/dust, MOEs range from 920 to 4,600; when assuming a ratio of 50/50 liquid/dust, MOEs range from 1,800 to 9,100; and when assuming a ratio of 99/1 liquid/dust, MOEs range from 91,000 to 450,000 (LOC = 300).

*Dust/Powder and Pump/Trigger Spray*: All residential handler (adults) non-cancer steady state inhalation risks estimated for the TCVP pet dust/powder pump/trigger spray formulations are not of concern (i.e., all MOEs are > 300; LOC = 300; range = 3,200 to 160,000).

A summary of residential handler exposures and risks is presented in Appendix G.

Residential Handler Cancer Exposure and Risk Estimate Equations

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[22] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

[23] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a Lifetime Average Daily Dose (LADD) is first calculated and then compared with a $Q_1$* that has been calculated for TCVP based on dose response data in the appropriate toxicology study ($Q_1$* = 1.83 x $10^{-3}$ (mg/kg/day)$^{-1}$). Absorbed average daily dose (ADD) levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the $Q_1$* to obtain cancer risk estimates.

The exposure data and assumptions that underlie the residential handler cancer risk estimates can be found in the 2014 residential assessment[24] and the 2012 Residential SOPs. The algorithms used to estimate the LADD and cancer risk for residential handlers can be found in Appendix B of the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833).

Summary of Residential Handler Cancer Exposure and Risk Estimates

*Pet Collars:* Residential handler cancer risks (combined dermal and inhalation) estimated for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio are all $10^{-7}$. When assuming a 50/50 liquid/dust formulation ratio (use of liquid-specific and dust-specific UE data) are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$.

*Dust/Powder and Pump/Trigger Spray*: Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$.

A summary of residential handler cancer exposures and risks is presented in Appendix H.

## 6.2 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of contacting a cat/dog previously treated with TCVP pet products (dusts/powders, pump/trigger sprays, pet collars). The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenario:

1) Post-application incidental oral (hand-to-mouth) exposure (children 1 to < 2 years olds only) from contacting cats and dogs treated with TCVP.

Since there is no non-cancer dermal hazard for TCVP, a quantitative non-cancer post-application dermal exposure assessment was not performed for adults or children. A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from applications to pets.

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[24] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

The lifestages selected for each post-application scenario (i.e., children 1 to < 2 years old) are based on an analysis provided as an Appendix in the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833) and the 2012 Residential SOPs.[25] While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Non-Cancer Post-Application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential non-cancer post-application risk assessment. The exposure data and assumptions that underlie the residential non-cancer post-application risk estimates can be found in the 2014 residential assessment[26] and the 2012 Residential SOPs.

Several inputs and assumptions that underlie the residential post-application risk assessment of TCVP pet products were addressed previously by EPA in the responses to NRDC's August 5, 2015 Opening Brief,[27] including: the use of the Davis study; TCVP pet collar product formulation type; daily exposure time spent in contact with TCVP treated pets; indirect hand-to-mouth activity; and the application of transferable residue data in EPA's risk assessment algorithms. NRDC has repeated all of these same arguments in its comments submitted for the 2015 DRA. EPA has addressed the use of the Davis study and TCVP pet collar product formulation type arguments herein. The agency's responses to all other arguments remain the same as addressed previously.

*Residue Transfer Assumptions:* Chemical-specific residue transfer studies were used for assessment of post-application exposures from registered TCVP pet products.

*Dust/Powder and Pump/Trigger Spray:* Consistent with the 2015 draft ORE assessment for Registration Review, a TCVP powder and pump spray study (MRID 45485501) was used to assess post-application exposure for these scenarios. A summary and discussion of the use of these data was included in the 2014 residential risk assessment. As described in the 2014 residential risk assessment, the TCVP powder and pump spray post-application exposure study was not conducted in a manner reflective of current standards that require a defined stroking procedure and greater number of petting simulations. In order to account for this difference, the agency used the maximum observed percent residue transfer on the day of product application (Day 0) for both formulations for exposure and risk quantification. Typically, the agency assesses post-application risk with use of the mean percent residue transfer measured on Day 0;

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[25] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[26] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

[27] W. Britton, Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589.

the use of the maximum value results in a more health protective risk assessment. Even though the post-application exposure study methods have evolved, the TCVP study employed a rigorous collection method and is not anticipated to underestimate exposure.

The 2012 Residential SOPs: Treated Pets recommends assessment of post-application exposures using day of application (i.e., Day 0) residue transfer -- defined as fraction application rate ($F_{AR}$) in the 2012 SOPs. Day of application (Day 0) percent residue transfer values used in the 2014 residential risk assessment for exposure/risk quantification of dusts/powders and pump/triggers sprays are as follows: dusts/powders, 0.048% (maximum observed) and pump sprays, 0.81% (maximum observed).

*Pet Collar Exposure Data Source:* The 2015 draft ORE assessment for Registration Review used both the Davis study and an amitraz pet collar residue transfer study for assessment of non-cancer residential post-application risks following contact with pets treated with TCVP pet collars. The Davis study publication was considered for use in the assessment due to arguments submitted by NRDC in its August 5th, 2015, Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.) (Opening Brief). NRDC's Opening Brief was filed in litigation challenging EPA's Nov. 6, 2014 denial of NRDC's 2009 petition to cancel all TCVP pet products; the denial was based on the 2014 residential pet product assessment. The agency provided a point-by-point response to the NRDC's arguments in a Dec. 21, 2015 memorandum,[28] issued in conjunction with the Dec. 21, 2015 Draft TCVP Risk Assessment for Registration Review. Among the arguments presented by NRDC was that the agency "failed to consider the Davis study for the estimation of post-application risks for exposures to the TCVP pet collar." In its 2015 memorandum, the agency acknowledged consideration of the potential effect of using the Davis study as the basis for residential post-application assessment of exposures from TCVP pet collars, the study was reviewed,[29] an OPP ethics review was conducted[30], and preliminary risk estimates were presented with use of these data. However, the formal use of the Davis study was put on hold pending review by EPA's HSRB in January 2016. The Davis study includes 1) glove residue data collected by adult volunteers petting TCVP treated dogs 2) plasma cholinesterase (ChE) measures from treated dogs 3) tee shirt samples collected from children exposed to TCVP treated dogs and 4) urinary biomonitoring for adults and children exposure to TCVP treated dogs. However, for purposes of the TCVP risk assessment, EPA may rely only on the transferable residue data [in light of 40 CFR Part 26, subpart Q regarding ethical standards for assessing whether to rely on the results in human research in EPA actions] as these are the only data from the study that result in the potential for greater risks, are applicable to human exposures (in the case of the dog plasma ChE measures), or in the case of the urinary biomonitoring data, are useful given current scientific limitations (i.e., a physiologically based pharmacokinetic (PBPK) model applicable to TCVP). While EPA proposed to rely only on the

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[28] W. Britton. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589.

[29] W. Britton. Science Review of "Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos" for HSRB Consideration. D430707. 12/16/2015.

glove residue data (which did not involve children), since these data were collected as part of broader research which did involve children, HSRB review was necessary.

On January 12-13, 2016, the EPA HSRB addressed the scientific and ethical charge questions related to Davis study. Ethics and science reviews were conducted by the agency in support of the HSRB meeting.[30,31] A Federal Register (FR) notice was published on 4/11/2016 (69 FR 21335) and provides the following information: EPA's proposal to rely on the Davis study; the reason for review by HSRB; the background on ethical conduct of research; summary of discussion on ethics-related questions; the standards applicable to ethical conduct and reliance on data; and the availability of HSRB meeting materials.[32]

The HSRB concluded that, "The research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol used in the study can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars."[33] Per EPA's response to NRDC's Opening Brief arguments, "EPA would rely on these data (Davis study) for regulatory decision making if HSRB determines that the study is scientifically valid and it meets appropriate human ethics requirements," since these data result in greater potential risks than those estimated using the amitraz pet collar residue transfer study (which had been relied upon in the previous risk assessments). Accordingly, post-application risks have been assessed with use of the Davis study data only and are presented herein.

The use of the Davis study as the primary data source is consistent with, and supported by, the recommendations from the comments following the 2015 draft ORE assessment for Registration Review including those submitted by NRDC and the Hartz Mountain Corporation. Per NRDC, "the Davis Study has met the appropriate scientific and ethical criteria and should be relied upon for the evaluation of exposures from TCVP containing flea collars," and the Hartz Mountain Corporation describes that, "the glove residue data measured in the Davis et al. (2008) study are valuable because they represent actual measurements of TCVP transfer from dogs wearing commercial collars to the hands of individuals petting them." Further, NRDC states that, "EPA's utilization of transferable residue data from the amitraz study is not supported by the evidence and should not be relied upon to evaluate risk."

A summary of the Davis study and a description of how these data have been used for risk quantitation is detailed in Section 5.2 of the corresponding ORE memo (D436833).

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[30] M. Lydon. Ethics Review of Davis et al Research on Flea Collars with TCVP. 12/15/2015.

[31] W. Britton. Science Review of "Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos" for HSRB Consideration. D430707. 12/16/2015.

[32] https://www.federalregister.gov/documents/2016/04/11/2016-08281/tetrachlorvinphos-tcvp-epa-proposal-to-rely-on-data-from-human-research-on-tcvp-exposure-from-flea

[33] Letter from Liza Dawson, PhD, Chair of the EPA HSRB to Thomas Burke, PhD, MPH, EPA Science Advisor. Subject: January 12-13, 2016 EPA Human Studies Review Board Meeting Report. March 30, 2016.

Residential Non-Cancer Post-application Exposure and Risk Equations

The algorithms used to estimate non-cancer exposure and dose for residential post-application can be found in Appendix B of D436833 and the 2012 Residential SOPs.

Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates

*Pet Collars:* As noted above, the post-application assessments for the TCVP pet collars were performed assuming pet collars could be either liquid or solid (dust) formulations, and assuming a varying liquid/dust exposure potential. All child 1 to <2 years old incidental oral exposures to pets treated with pet collars, regardless of the ratio of liquid/dust assumed, are estimated to be of concern (i.e., MOEs < 1000). When assuming a 1/99 liquid/dust formulation ratio, MOEs range from 0.91 to 7.4. When assuming a 50/50 liquid/dust formulation, MOEs range from 1.8 to 15, and when assuming a 99/1 liquid/dust formulation, MOEs range from 65 to 530. A summary of residential post-application exposures and risks from TCVP pet products is presented in Appendix I.

*Dust/Powder and Pump/Trigger Spray*: Residential post-application steady state non-cancer child 1 to < 2 years old incidental oral (hand-to-mouth) exposures to pets treated with TCVP dust/powders are estimated to be of concern (i.e., MOEs < 1000; MOE range from 98 to 640). However, child 1 to < 2 years old incidental oral exposures to pets treated with TCVP pump/trigger spray products are estimated not to be of concern (i.e., MOEs are > 1,000; MOE range from 1,600 to 15,000).

Residential Cancer Post-Application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential cancer post-application risk assessment. All exposure data and assumptions that underlie the residential post-application cancer risk estimates can be referenced in the 2014 residential assessment. Note: For purpose of quantification of estimated TCVP post-application cancer risks, HED used average percent residue transfer data for all days sampled from chemical-specific exposure data for all pet formulations assessed (i.e., the TCVP powder and pump spray study and the Davis study).

Residential Cancer Post-application Exposure and Risk Estimate Equations

As was done for residential handlers, cancer post-application risk estimates for adults were calculated using a linear low-dose extrapolation approach in which a LADD is first calculated and then compared with a $Q_1$* that has been calculated for TCVP based on dose response data in the appropriate toxicology study ($Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$). The algorithms used to estimate the LADD and cancer risk for residential post-application exposure can be found in Appendix B of D436833.

It should be noted that in the past, cancer risk assessments have assumed that children are no more sensitive than adults to carcinogens (i.e., no adjustment was made to children's exposure estimates in calculating a cumulative lifetime exposure). More recently, the agency's

"Guidelines for Carcinogen Risk Assessment" (USEPA, 2005) and "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens" (USEPA, 2005) proposed age-dependent adjustment factors to be applied to children's exposure. These age-dependent factors are applied only to carcinogens shown to have a mutagenic mode of action. In general, most carcinogenic pesticides have not been shown to act through a mutagenic mode of action, and thus separate assessment of children and adults is not warranted. Any pesticide found to be a carcinogen acting through a mutagenic mode of action should be dealt with on a case by case basis, and such an assessment should follow the agency's 2005 guidance. Once the results of the newly-required mutagenicity studies have been submitted and reviewed, the need for an updated cancer assessment will be determined.

Summary of Residential Post-application Cancer Exposure and Risk Estimates

*Pet Collars:* Residential cancer (adult only) risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio range from $10^{-5}$ to $10^{-4}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1 liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$.

*Dust/Powder and Pump/Trigger Spray:* Residential cancer (adult only) risks estimated for TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$.

Adult residential post-application dermal cancer risk estimates are presented in Appendix J.

## 6.3 Spray Drift

A quantitative spray drift assessment was not conducted because the use of TCVP for direct animal treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs are either 1) not applied via aircraft, groundboom, or airblast equipment or 2) for applications to poultry buildings with groundboom equipment, the use is indoors and not anticipated to be a significant source of spray drift.

## 6.4 Residential Bystander Post-Application Inhalation Exposure

A quantitative residential post-application inhalation exposure assessment was not performed, as inhalation exposure is expected to be negligible from applications to pets.

# 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, for food use pesticides, aggregate risk assessment must consider exposures from three sources: food, drinking water, and residential uses. These exposures could occur from three major routes: oral, dermal, and inhalation. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating



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exposures and risks from various sources, HED considers both the route and duration of exposure.

## 7.1 Acute Aggregate Risk

The acute aggregate risk assessment combines exposures to TCVP from food and drinking water. While drinking water exposures alone were not of concern, there are acute risk estimates of concern for food only; therefore, a quantitative acute aggregate risk assessment was not conducted.

## 7.2 Steady State Aggregate Risk

The steady state aggregate assessment includes the steady state dietary (food and water) and residential exposures. However, because there are risks of concern associated with both dietary (food) and residential exposure, a quantitative steady state aggregate risk assessment was not conducted.

## 7.3 Cancer Aggregate Risk

The cancer aggregate risk assessment combines residential and dietary (food and drinking water) expected lifetime exposures for adults. For TCVP, a cancer aggregate assessment was performed for adult handlers and for adult post-application activities related to residential pet product use.

The residential handler cancer aggregate assessment uses exposures from applying TCVP products to pets (collars, dust/powders, and pump/trigger sprays). Residential handler cancer (dermal) risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio are all $10^{-7}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$. Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$. The cancer dietary (food and drinking water) assessment resulted in an estimated risk of $9 \times 10^{-7}$. The cancer aggregate assessment combines the highest (worst case) handler exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type.

The cancer aggregate (dietary and residential exposures) risk estimates for handlers are in the $10^{-7}$ to $10^{-6}$ range and are presented in Table 7.3.1.

The residential post-application cancer aggregate assessment uses dermal exposures from contacting pets treated with TCVP products (collars, dust/powders, and pump/trigger sprays). Residential cancer post-application risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio range from $10^{-5}$ to $10^{-4}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1



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liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$. Post-application cancer risks estimated for handlers of the TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$. The cancer aggregate assessment combines the highest (worst case) post-application exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type.

The cancer aggregate (dietary and residential exposures) post-application risk estimates are in the $10^{-6}$ to $10^{-4}$ range and are presented in Table 7.3.2.

**Table 7.3.1. Adult Handler Aggregate Cancer Risk Estimates for TCVP Pet Products**
***(Risk is estimated using a Q* of 0.00183)***

| Product Formulation Type | Reg No.; Animal type; Animal size | Food and Water Exposure (mg/kg/day)[1] | Residential Exposure (LADD, mg/kg/day)[2] | Aggregate Cancer Risk (food, water, residential) |
|---|---|---|---|---|
| **Pet Collar** (1/99 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $1.1 \times 10^{-4}$ | $1 \times 10^{-6}$ |
| **Pet Collar** (50/50 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $5.9 \times 10^{-5}$ | $1 \times 10^{-6}$ |
| **Pet Collar** (99/1 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $8.5 \times 10^{-6}$ | $9 \times 10^{-7}$ |
| **Dust/Powder** | 67517-82: Dog; Large | $5.1 \times 10^{-4}$ | $2.3 \times 10^{-4}$ | $1 \times 10^{-6}$ |
| **Pump/Trigger Spray** | 2596-125, -140: Dog (Trigger); Large | $5.1 \times 10^{-4}$ | $3.9 \times 10^{-5}$ | $1 \times 10^{-6}$ |

[1] Table 5.4.5.1
[2] Appendix D of ORE Memo D436833.
[3]Aggregate Cancer Risk = ($Q_1$*) (Food & Water Exposure + Residential LADD)

**Table 7.3.2. Adult Post-Application Aggregate Cancer Risk Estimates for TCVP Pet Products**
***(Risk is estimated using a Q* of 0.00183)***

| Product Formulation Type | Reg No.; Animal type; Animal size | Food and Water Exposure (mg/kg/day)[1] | Residential Exposure (LADD, mg/kg/day)[2] | Aggregate Cancer Risk (food, water, residential) |
|---|---|---|---|---|
| **Pet Collar** (1/99 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $3.4 \times 10^{-1}$ | $6 \times 10^{-4}$ |

| Table 7.3.2. Adult Post-Application Aggregate Cancer Risk Estimates for TCVP Pet Products *(Risk is estimated using a Q* of 0.00183)* | | | | |
|---|---|---|---|---|
| **Product Formulation Type** | **Reg No.; Animal type; Animal size** | **Food and Water Exposure (mg/kg/day)[1]** | **Residential Exposure (LADD, mg/kg/day)[2]** | **Aggregate Cancer Risk (food, water, residential)** |
| **Pet Collar** (50/50 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $1.8 \times 10^{-1}$ | $3 \times 10^{-4}$ |
| **Pet Collar** (99/1 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $1.6 \times 10^{-2}$ | $3 \times 10^{-5}$ |
| **Dust/Powder** | 2596-78: Cat; Small | $5.1 \times 10^{-4}$ | $1.9 \times 10^{-3}$ | $2 \times 10^{-6}$ |
| **Pump/Trigger Spray** | 2596-126, 140: Cat (Trigger); Small | $5.1 \times 10^{-4}$ | $5.3 \times 10^{-4}$ | $2 \times 10^{-6}$ |

[1] Table 5.4.5.1
[2] Appendix F of ORE Memo D436833.
[3]Aggregate Cancer Risk = ($Q_1$*) (Food & Water Exposure + Residential LADD)

## 8.0 Occupational Exposure/Risk Characterization

Occupational and Residential Exposure Memo: D436833, 12/21/2016, W. Britton.

Occupational handler risks have been updated herein to reflect changes in the policy used for inhalation assessment since the 2015 ORE assessment. Previously, HED was using multiple human equivalent doses (HEDs) specific to different handler activities. The current policy recommends that only a single HED is necessary to assess all potential occupational handler activities. All other occupational handler data, assumptions, and algorithms used for the 2015 ORE assessment remain the same.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

### 8.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

***Mixer/Loaders:***

(1a) Liquid: Groundboom Applications
(1b) Liquid: Paint Applications
(2a) Wettable Powder: Groundboom Applications
(2b) Wettable Powder: Paint Applications
(3a) Dust: Paint Applications

***Applicators:***

(4) Groundboom Applications
(5) Open Pour Liquid Additive for Feed Through
(6a) RTU Pet Collar – 1/99 Liquid/Dust Formulation
(6b) RTU Pet Collar – 50/50 Liquid/Dust Formulation
(6c) RTU Pet Collar – 99/1 Liquid/Dust Ratio Formulation
(7) RTU Dust/Powder – Pets
(8) RTU Pump/Trigger Sprays - Pets

***Mixer/Loader/Applicators:***

(9a) Liquid: Backpack Sprayer
(9b) Liquid: Manually-Pressurized Handwand
(9c) Liquid: Mechanically-Pressurized Handgun
(9d) Liquid: Backrubber or Facerubber
(10a) Wettable Powder: Backpack Sprayer
(10b) Wettable Powder: Manually-Pressurized Handwand
(10c) Wettable Powder: Mechanically-Pressurized Handgun
(10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary)
(10e) Wettable Powder: Rotary Duster
(10f) Wettable Powder: Plunger Duster
(11a) Dust: Self-Treating Dust Bag
(11b) Dust: Shaker Can
(11c) Dust: Rotary Duster
(11d) Dust: Plunger Duster
(12a) Paint: Brush or Roller
(12b) Paint: Airless Sprayer
(13) Solid Feed Additive for Feed Through: Cup

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis. Application rate: A summary of all TCVP occupational use sites and application rates is presented in Appendix A of D436833.

*Pet Collar Formulation Assumptions:* As was mentioned in the residential sections, due to the uncertainty associated with whether TCVP pet collars are liquid and/or dust formulated products, handler steady state inhalation exposures for TCVP pet collar application were assessed assuming pet collars could be liquid and solid (dust) formulations concurrently with varying ratios of liquid/dust. The liquid formulation UE data assumes negligible inhalation exposure; therefore, only the dust-specific UE data is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure.

*Unit Exposures:* It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[34]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the agency website[35].

A single chemical-specific exposure study, Monitoring Exposure of Mixer/Loaders and Applicators Treating Agricultural Premises with Tetrachlorvinphos (Rabon® 50 WP Insecticide) in Handheld Wand-Type Sprayers (MRID 42622301), was used as appropriate (i.e., exposure scenario 10c, mix/load and apply WP with mechanically-pressurized handgun) in the most recent occupational risk assessment for TCVP.[36] Per the prior risk assessment, risks for the exposure scenario were estimated with use of the chemical-specific exposure data as well as surrogate PHED data. This exposure study was summarized in the 2015 draft ORE assessment Registration Review[37].

The PHED data recommended for the exposure scenario reflects unit exposure values (dermal and inhalation) that represent an individual conducting all activities, mixing/loading/applying, for use of the WP product by mechanically pressurized handgun. In contrast, the chemical-specific exposure study was conducted in a manner which separated out the mixing/loading and application components of the exposure scenario. Exposure scenario 10c has been assessed, and estimated risks presented separately, (i.e., mixer/loader and applicator) with use of the chemical-specific data, and for all activities with use of PHED. When applied, the dermal and inhalation unit exposures resulting for product application result in risk estimates that are very similar to risk estimates using the PHED data. Non-cancer and cancer private/farmer and

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[34] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[35] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html
[36] J. Dawson. Tetrachlorvinphos: Further Revisions to Occupational Risk Assessment for Uses in the Poultry and Cattle Production Industries. 3/28/2002. D281972.
[37] W. Britton. Tetrachlorvinphos: Occupational and Residential Exposure Assessment for Registration Review. 12/21/2015. D426984.

contract/commercial occupational handler risk estimates for exposure scenario 10c are presented separately from the risk summaries for all other occupational handler exposure scenarios in Appendix K: Table K.2 and Appendix L: Tables L.2 and L.4, respectively.

In some cases, due to the lack of data for an exposure scenario or the unique nature of the scenario, surrogate exposure data were used as follows:

- Exposure data for the loading/application of dust formulations were used as a surrogate for the loading/application of wettable powders for rotary and plunger duster applications (10e, 10f). For exposure scenario 10e, exposure data for plunger dusters were used due to the lack of data for the rotary duster application method.
- For the assessment of pet collars as a dust formulation, data for applying dusts using a shaker can were used as a surrogate.
- Unlike more typical exposure scenarios where a RTU paint is only loaded or applied, for TCVP the paint must be mixed/loaded for the liquid (1b), wettable powder (2b), and dust (3a) formulations. These exposure scenarios were assessed using the exposure data appropriate for mixing/loading for each formulation with the exception of dust where WP formulation was used as a surrogate for dust.
- For TCVP applications to livestock with a dust formulation via shaker can, a RTU product is not available; therefore, exposures from the mixing/loading of the dust formulation must be assessed in addition to potential exposure resulting from application via shaker can. As a result, the exposure data for the loading/application via a RTU shaker can was used for the assessment of all scenarios relating to the use. The use of these data results in a more protective assessment than would be if the mixing/loading of the dust were assessed separately.
- Exposures from the application of feed (salt or mineral) blocks in livestock – typically, 5 – 15 per head of cattle or horses – is assumed to be negligible if gloves are worn when placing the blocks. Furthermore, for these products the greater majority of the active ingredient is contained within the block, thus further reducing the exposure potential.

*Area Treated or Amount Handled:* The following inputs are consistent with those used in the most recently conducted occupational risk assessment for TCVP and, for those inputs relating to the poultry industry, are reflective of research conducted by BEAD at that time.

- Groundboom: 100,000 square feet for applications to poultry buildings
- Backpack and manually pressurized handwand: 20,000 square feet for applications to poultry buildings
- Mechanically pressurized handwand: 100,000 square feet for applications to poultry buildings
- Backpack, handheld/stationary fogger, manually pressurized handwand, mechanically pressurized handwand, rotary spreader: 20,000 birds for direct application to poultry (i.e., approximately 1 square foot/bird)
- Backrubber/facerubber: 50 gallons
- Paint applications: 2 gallons



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The following inputs are based on either the most recently conducted permethrin occupational and residential exposure and risk assessment for similar use patterns[38] or best professional judgment of product usage:

- All handheld equipment: 400 animals treated daily
- Handheld/stationary fogger: 100,000 square feet to poultry buildings
- Plunger, shaker can, spoon: 1,000 birds or 1,000 square feet
- Pet collar, pump/trigger spray, and shaker can applications: 8 animals treated daily
- Self-treating dust bags: 10 filled daily (assuming a 12.5 lb dust bag)

The following inputs are consistent with EPA regulatory definitions for large concentrated animal feeding operations (CAFOs)[39]. The inputs assume that a single individual is responsible for the food preparation for the entire CAFO and applies the TCVP feed-through products to the animal feed.

- Cup, pour on: 1,000 cows, 500 horses, and 6,250 pigs for liquid and solid feed-through applications. The number of cows and horses represents the maximum identified for large CAFO operations. The number of pigs was estimated by averaging the maximum number weighing over 55 lbs (2,500) and less than 55 lbs (10,000) in large CAFO operations.

*Exposure Duration*: Occupational handler exposure is expected to be short- and intermediate-term in duration. Because of the steady state AChE inhibition exhibited by the OPs, steady state exposures (typically 21 days and longer for OPs, but 1 day to reach steady state for tetrachlorvinphos) were assessed and presented for occupational exposures to TCVP products.

*Mitigation/Personal Protective Equipment:* Estimates of non-cancer inhalation exposure were calculated for various levels of PPE (i.e., respiratory protection). Results are presented for no respirator, PF5 respirator, PF10 respirator, or engineering controls (EC).

The PPE required for occupational use of TCVP varies by formulation type. The respiratory protection required for the occupational handling of TCVP can, at times, differ from label to label with consideration of the same formulation and exposure scenario. Occupational handler exposures are expected from use of TCVP on livestock and pets by livestock handlers, veterinarians, veterinary assistants, and groomers. The pet use formulations include collars, dusts/powders, and pump and trigger sprays. All but one of the TCVP pet product labels do not require PPE, as these are intended for residential sale as well as for occupational use. A summary of PPE required for all TCVP products is presented in Appendix A of D436833.

*Days per Year of Exposure:* To assess cancer risk, it is assumed that private/farmers would be exposed 10 days per year and commercial applicators would be exposed 30 days per year. The

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[38] C. Smith. Permethrin: Third Revision of the Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. 4/4/2006. D325428.
[39] http://www.epa.gov/npdes/pubs/sector_table.pdf

term "private/farmer" means that the applicators or one of the workers would apply the pesticides to land owned or operated by the farmer. Commercial applicators mean the applicators are completing multiple applications for multiple clients.

*Years per Lifetime of Exposure:* It is assumed that handlers would be exposed for 35 years out of a 78-year lifespan.

*Lifetime Expectancy:* Life expectancy values are from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males was 75 years and 80 years for females. Based on the available data, the recommended value for use in cancer risk assessments is 78 years.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix B of D436833.

Combining Exposures/Risk Estimates

Although occupational dermal and inhalation exposures are anticipated for TCVP, risks have been estimated for inhalation exposures only due to the lack of dermal hazard. Therefore, no combined occupational exposures/risk estimates have been quantified.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Of the 198 total occupational handler exposure scenarios assessed, the majority (162) are not of concern (i.e., steady state inhalation MOEs are $\geq$ 300) with currently required personal protective equipment (PPE) (i.e., respiratory protection). Of the remaining 36 handler exposure scenarios, 25 are not of concern with consideration of increasing levels of respiratory protection (i.e., 11 occupational handler exposure scenarios result in estimated risks of concern despite the addition of respiratory protection or engineering controls; MOEs at highest level of respiratory protection range from 3.9 to 280). These eleven handler scenarios include dust formulations (mixing/loading/applying TCVP by rotary duster, self-treating dust bag, or shaker can) and wettable powder formulations (mixing/loading/applying TCVP by mechanically-pressurized handgun using MRID 42622301 and mixing/loading/applying using fogging equipment).

A summary of all non-cancer occupational handler exposure scenarios is presented in Appendix K. For risk management purposes, the currently labeled level of respiratory protection and EC has been identified (shaded) for each individual exposure scenario.

Occupational Handler Cancer Exposure and Risk Equations

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which an LADD is first calculated and then compared with a Q1* that has been calculated for TCVP based on dose response data in the appropriate toxicology study (Q1* = $1.83 \times 10^{-3}$ (mg/kg/day)-1). ADD levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the Q1* to obtain cancer risk estimates. The algorithms used to

estimate the LADD and cancer risk for occupational handlers can be found in Appendix B of D436833.

Summary of Occupational Handler Cancer Exposure and Risk Estimates
Occupational cancer risks were estimated for both private/farmer and contract/commercial handlers. Cancer risks, with currently required PPE, range from $10^{-10}$ to $10^{-5}$ for private/farmer handlers and from $10^{-10}$ to $10^{-4}$ for contract/commercial handlers with currently required PPE.

Unlike the occupational handler non-cancer risk estimates which were based only on inhalation exposures, the occupational handler cancer risk estimates are quantified based on both dermal and inhalation exposures. This is because, despite the determination of the lack of dermal hazard for TCVP, dermal exposures from TCVP must be quantified for the purpose of cancer risk assessment. As previously described, the PPE required for the occupational use of TCVP varies by formulation type. For example, for feed through (solid and liquid food additives) and feed blocks, occupational handlers are required to wear baseline clothing (i.e., long sleeved shirt, long pants, shoes and socks) and gloves. For all other end-use labels with livestock and outdoor perimeter uses, required PPE can vary dependent on the application type or equipment and can range from baseline clothing and gloves, to the addition of coveralls, or respiratory protection.

A summary of occupational cancer risks as estimated at all levels of personal protection and with use of engineering controls is presented in Appendix L. Tables L.1 and L.2 present cancer risks for private/farmer handlers and Tables L.3 and L.4 risks for contract/commercial handlers. For risk management purposes, the currently labeled level of respiratory protection and EC has been identified (shaded) for each individual exposure scenario.

## 8.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties.

Occupational post-application exposures are not anticipated for TCVP as the majority of application scenarios are not to foliar surfaces. The use of TCVP outdoors as a perimeter treatment is not expected to result in occupational post-application exposure as reentry activities related to crop production (e.g., scouting, harvesting) are not anticipated for this use pattern.

# 9.0 Public Health and Pesticide Epidemiology Data

Incident Report Memo: D426986, 5/21/15, S. Recore [40]

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[40] S. Recore *et al.*, 5/21/2015, D426986, Tetrachlorvinphos (TCVP): Tier I Review of Human Incidents for Draft Risk Assessment

HED has prepared a Tier I review of human incidents report. For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient TCVP. The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to TCVP exposure.

The Agricultural Health Study (AHS) is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. TCVP is not included in the AHS, and therefore this study does not provide information for this report.

Although there were a moderate number of TCVP incidents reported to Main and Aggregate IDS (n=374) and SENSOR-Pesticides (n=61), most of these incidents were classified as low severity. The effects experienced were generally minimally traumatic and resolving rapidly and usually involve skin, eye or respiratory irritation. Most of the reported incidents were due to handling and applying TCVP products to pets. Based on the low severity of incident cases reported for TCVP in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. The agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

## 10.0 Cumulative Exposure/Risk Characterization

OPs, like TCVP, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PoDs for each OP, including TCVP. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.5, OPP has retained the FQPA Safety Factor for OPs, including TCVP, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes.

The agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to release of the revised risk assessment. During this period, the agency will determine whether or not it is appropriate to apply the draft guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis for the neurodevelopment outcomes.

## 11.0 Appendices

Appendix A. Toxicology Profile
Appendix B. Results for BMD/BMDL modeling for TCVP
Appendix C. Methodologies for HEC Calculations
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## Appendix A. Toxicology Profile and Executive Summaries

### A.1. Toxicology Data Requirements

The requirements (40 CFR 158.500) for the food use for TCVP are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

| Study | Technical | |
|---|---|---|
| | Required | Satisfied |
| 870.1100 Acute Oral Toxicity | yes | yes |
| 870.1200 Acute Dermal Toxicity | yes | yes |
| 870.1300 Acute Inhalation Toxicity | yes | yes |
| 870.2400 Primary Eye Irritation | yes | yes |
| 870.2500 Primary Dermal Irritation | yes | yes |
| 870.2600 Dermal Sensitization | yes | yes |
| 870.3100 90-Day Oral Toxicity in Rodents | yes | yes |
| 870.3150 90-Day Oral Toxicity in Non-rodents | yes | yes [a] |
| 870.3200 21/28-Day Dermal | yes | yes |
| 870.3250 90-Day Dermal | no | - |
| 870.3465 90-Day Inhalation | yes | yes [b] |
| 870.3700a Prenatal Developmental Toxicity in Rodents | yes | yes |
| 870.3700b Prenatal Developmental Toxicity in Non-rodents | yes | yes |
| 870.3800 Reproduction | yes | yes |
| 870.4100a Chronic Toxicity in Rodents | yes | yes |
| 870.4100b Chronic Toxicity in Non-rodents | yes | yes |
| 870.4200a Carcinogenicity in Rats | yes | yes |
| 870.4200b Carcinogenicity in Mice | yes | yes |
| 870.4300 Chronic Toxicity/Carcinogenicity in Rats | yes | yes |
| 870.5100 Mutagenicity—Bacterial Reverse Mutation Test | yes | yes |
| 870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test | yes | yes |
| 870.5375 Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.5xxx Mutagenicity—Other Genotoxic Effects | yes | no[c] |
| 870.6100a Acute Delayed Neurotoxicity in Hens | yes | yes |
| 870.6100b 90-Day Neurotoxicity in Hens | yes | yes |
| 870.6200a Acute Neurotoxicity Screening Battery in Rats | yes | yes |
| 870.6200b 90-Day Neurotoxicity Screening Battery in Rats | yes | yes |
| 870.6300 Develop. Neurotoxicity | yes | yes |
| 870.7485 General Metabolism | yes | yes |
| 870.7600 Dermal Penetration | yes | yes |
| 870.7800 Immunotoxicity | yes | yes |
| Special Studies<br>Comparative Cholinesterase in Rats | yes | yes |

[a] there is a chronic study; [b] 4-Week study

[c] A follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and a study that investigates possible genotoxic activity in the target organ (liver) are required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target).



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## A.2 Toxicity Profiles

| Table A.2.1 Acute Toxicity of Tetrachlorvinphos Technical | | | | |
|---|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No.** | **Results** | **Toxicity Category** |
| 870.1100 | Acute Oral – Rat | 41222504 | $LD_{50}$ =<br>1480 mg/kg (M)<br>465-965 mg/kg (F) | III |
| 870.1200 | Acute Dermal – Rabbit | 41222505 | $LD_{50}$ > 2000 mg/kg | III |
| 870.1300 | Acute Inhalation – Rat | 00138933 | LC50 > 3.61mg/L | IV |
| 870.2400 | Acute Eye Irritation - Rabbit | 41222506 | moderate | III |
| 870.2500 | Acute Dermal Irritation - Rabbit | 41222507 | slight | IV |
| 870.2600 | Skin Sensitization - Guinea Pig | 41377902<br>42981001 | sensitizer | N/A |
| 870.6100 | Acute Delayed Neurotoxicity | 41905901 | No clinical signs of neurotoxicity observed (NTE not measured) | N/A |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3100<br>21-Day Oral Toxicity in (Crl:CD®(SD)IGS BR rats) | 45570601<br>(2001)<br>Acceptable/non-guideline (21-day study; gavage)<br>0, 8, 12, 20, or 50 mg/kg/day | **Repeat exposure**:<br>Brain ChEI NOAEL = 12 mg/kg/day<br>Brain ChEI LOAEL = 20 mg/kg/day, based on brain cholinesterase activity inhibition in females (day 21).<br><br>RBC ChEI NOAEL = 8 mg/kg/day<br>RBC ChEI LOAEL = 12 mg/kg/day, based on RBC cholinesterase activity inhibition in males and females<br>***HIARC: RBC data not reliable***<br>**Single dose exposure**:<br>RBC ChEI NOAEL = 20 mg/kg.<br>RBC ChEI LOAEL = 50 mg/kg, based on RBC cholinesterase activity in both sexes.<br>NOTE: *HIARC: RBC data not reliable from this study.*<br><br>Brain ChEI NOAEL =12 mg/kg.<br>Brain ChEI LOAEL = 20 mg/kg, based on brain cholinesterase activity inhibition (ChEI) in males (22%). At 50 mg/kg, males had 54% and females had 23% brain cholinesterase inhibition.<br><br>$BMDL_{10}$ = 6.7 mg/kg/day<br>$BMD_{10}$ = 9.9 mg/kg/day, based on female RBC ChE inhibition<br>$BMDL_{10}$ = 12.2 mg/kg/day<br>$BMD_{10}$ = 14.7 mg/kg/day, based on female brain ChE inhibition |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3150<br>90-Day Oral Toxicity<br>(Sprague Dawley rats) | 43371201 (1990)<br>Acceptable/guide line<br>0, 100, 2000, or 5000 ppm (diet)<br>Males: 0, 6.7, 142, and 375 mg/kg/day;<br>Females: 0, 10.0, 197, and 467 mg/kg/day.<br><br>$BMDL_{10}$ = 8.0 mg/kg/day<br>$BMD_{10}$ = 10.49 mg/kg/day, based on female RBC ChE inhibition | RBC ChEI NOAEL = 6.7 mg/kg/day<br>RBC ChEI LOAEL = 142 mg/kg/day, based on RBC ChEI in both sexes (males 30%*; females 79%**), bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females and mid-dose males, higher adjusted liver weights (both sexes), higher adjusted adrenal weights in females, and thyroid follicular cell hypertrophy in both sexes. At 467 mg/kg/day, in addition to RBC ChEI in both sexes (males 72%*; females 91%**), females had a 24% brain cholinesterase inhibition, although statistical significance was not attained (females 12%, 14%, 24% brain ChEI with increasing dose; males 1% at HDT). Additionally, decreased body weight was observed throughout the study in males (7%- 12%), with the magnitude of the deficit increasing over time.<br><br>$BMDL_{10}$ = 8.0 mg/kg/day<br>$BMD_{10}$ = 10.49 mg/kg/day, based on female RBC ChE inhibition<br>$BMDL_{10}$ = 26.3 mg/kg/day<br>$BMD_{10}$ = 61.6 mg/kg/day, based on male RBC ChE inhibition<br>No dose-response for brain ChE inhibition (BMD not run) |
| 870.3200<br>21/Day Dermal Toxicity (Crl:CD BR Sprague Dawley rat) | 41342001 (1989)<br>Acceptable/guide line<br>0, 10, 100, or 1000 mg/kg/day<br>6 hours/day, 5 days/week for 15 treatments over a 21-day period | NOAEL = 1000 mg/kg/day<br>LOAEL = not determined.<br>RBC and brain cholinesterase inhibition were not observed in either sex at dose levels up to and including the limit dose.<br><br>Significant dermal effects were not observed. There were no treatment-related effects on body weight, food consumption, hematology or clinical chemistry parameters (except plasma ChE activity), gross or microscopic pathology in either sex.<br>Plasma ChE inhibition was observed in females at 1000 mg/kg/day. |
| 870.3465<br>28-Day Inhalation Toxicity (Sprague-Dawley rat) | 48803501 (2012)<br>Acceptable/guide line<br>nose-only aerosol 6 hours/day, 5 days/week for 3 weeks at exposure concentrations of 0, 0.05, 0.5, or 1.0 mg/L; during the final week of exposure (week 4), the animals were exposed for 7 days | NOAEL= 0.05 mg/L/day<br>LOAEL = 0.5 mg/L/day, based on an increase in RBC cholinesterase inhibition in both sexes. *Brain cholinesterase activity was not monitored.*<br><br>Systemic NOAEL not identified.<br>Systemic LOAEL = 0.05 mg/L, based on diffuse adrenal cortical cell vacuolation in both sexes, enlarged adrenals in females, and increased adrenal weights in females. At 0.5 mg/L and 1.0 mg/L, in addition to the adrenal findings, there was a dose-related increase in vacuolation of the ovaries in females, an increase in squamous metaplasia of the larynx in both sexes, and an increase in follicular cell hyperplasia of the thyroids in both sexes.<br><br>**Sex/Age** \| **Compartment** \| **$BMD_{10}$** \| **$BMDL_{10}$**<br>Female \| RBC \| 0.394 \| 0.050<br>Male \| RBC \| 0.122 \| 0.022 |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3700a Prenatal developmental in (Sprague Dawley Crl:COBS®CD ® (SD)BR)<br><br>TXR# 008124, 008616, 018781 | 40152701 (1987)<br>41828001(1991)<br>41967201 (1991)<br>42520101 (1992)<br>Acceptable/guide line<br>0 (aqueous 0.5% methyl cellulose), 75, 150, or 300 mg/kg/day<br>GD 6-15; 10 mL/kg (gavage) | **Maternal** NOAEL = 75 mg/kg/day<br>**Maternal** LOAEL = 150 mg/kg/day, based on a reduction in BWG/FC*<br>At 300 mg/kg/day, there were clinical signs of toxicity (tremors and chromodacryorrhea)<br>**Developmental** NOAEL =300 mg/kg/day<br>**Developmental** LOAEL = not identified.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).*<br><br>*BWG not considered an adverse effect since BW was not affected. NOAL/LOAEL should be revised to 150/300 mkd. |
| 870.3700b Prenatal developmental in (New Zealand white rabbit) | 00127831 (1982)<br>Acceptable/guide line<br>0, 150, 375, or 750 mg/kg/day (1% CMC)<br>GD 6-19; 5 mL/kg (gavage) | **Maternal** NOEL = 375 mg/kg/day<br>**Maternal** LOEL = 750 mg/kg/day, based on mortality, abortions, and red vaginal fluid.<br>**Developmental** NOAEL = 375 mg/kg/day<br>**Developmental** LOAEL = 750 mg/kg/day, based on an increase in early resorptions and corresponding increase in post implantation loss, and a decrease in live fetuses/doe.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).* |
| 870.3800 Reproduction and Fertility Effects (Charles River CD Crl®SD) BR rats) | 42054301 (1991)<br>acceptable/guidel ine<br>0, 100, 500, or 2000 ppm (diet)<br>F0 Males 0, 5.2, 26, 102 mg/kg/day<br>F1 Males 0, 6.7, 34, 130 mg/kg/day<br><br>F0 Females 0, 7.3, 40, or 155 mg/kg/day<br>F1 Females 0, 8.3, 43, or 168 mg/kg/day | **Parental** NOAEL = 500 ppm (males 26/females 40 mg/kg/day)<br>**Parental** LOAEL = 2000 ppm (males 102/females 155 mg/kg/day), based on decreased body weight gain in F1 generation, increased adrenal weights of F0 females, and decreased body weight gains in F0 males.<br>**Offspring** NOAEL = 2000 ppm (males 102/females 155 mg/kg/day)<br>**Offspring** LOAEL was not identified.<br>**Reproductive** NOAEL = 2000 ppm (males 102/females 155 mg/kg/day)<br>**Reproductive** LOAEL was not identified.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).* |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4100a Chronic Toxicity (Sprague-Dawley rat) | 42980901 (1993)<br>43335101 (1994)<br>Acceptable/guideline<br>0, 100, 1000, or 2000 ppm (diet)<br>Males 0, 4.23, 43.2, or 88.5 mg/kg/day<br>Females 0, 5.93, 62.7, or 125.3 mg/kg/day<br>(2-year study) | NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes); reduced body weight; ~~plasma~~ cholinesterase inhibition in females.<br>RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **); brain ChEI in females at 52 and 104 weeks was 17% and 16% (not **).<br>NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on RBC cholinesterase inhibition in females<br><br>BMD not run due to lack of dose-response |
| 870.4100b Chronic toxicity (Beagle dog) | 42679401 (1993)<br>Acceptable/guideline<br>0, 0, 6.25, 500, 1000 mg/kg/day; (capsule)<br>4/sex/group<br>Cholinesterase pre-test, 12, 26, 52 weeks (plasma, RBC)<br>Brain at termination (1 year) | NOAEL = 6.25 mg/kg/day<br>LOAEL = 500 mg/kg/day, based on plasma cholinesterase inhibition (both sexes), decreased red blood cell counts, hemoglobin, hematocrit, MCHC, MCV, alkaline phosphatase, urine specific gravity, and decreased liver and kidney weights.<br>At 1000 mg/kg/day, increased white blood cell counts (females), increased prostate weight, decreased cholesterol (males).<br>RBC and brain cholinesterase inhibition were not observed at any dose level in either sexes. |
| 870.4200a Carcinogenicity (Sprague Dawley rat) | 42980901 (1993)<br>43335101 (1994)<br>acceptable/ guideline<br>0, 100, 1000, or 2000 ppm (diet)<br>Males 0, 4.23, 43.2, or 88.5 mg/kg/day<br>Females 0, 5.93, 62.7, or 125.3 mg/kg/day<br>104 weeks | NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes); reduced body weight; cholinesterase inhibition in females.<br>RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **); brain ChEI in females at 52 and 104 weeks was 17% and 16% (not **).<br>NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on RBC cholinesterase inhibition in females<br>BMD not run due to lack of dose-response<br>Increased incidence of thyroid C-cell adenomas in male rats at HDT and adrenal pheochromocytomas in males |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4200b Carcinogenicity (B6C3F1 mouse) | 00117443 (1978) Acceptable/guideline 0, 17.5, 64, 320, 1600, 8000, 16000 ppm 0, 2.6, 9.6, 48, 240, 1200, or 2400 mg/kg/day | NOAEL = 1600 ppm (240 mg/kg/day)<br>LOAEL = 8000 ppm (1200 mg/kg/day), based on decreased body weight gain<br>Statistically significant increases in combined hepatocellular adenoma/carcinoma (primarily carcinomas) in female B6C3F1 mice at 1600 ppm.<br>Other doses considered excessive; combined adenomas/carcinomas in males, renal adenomas/carcinomas and combined in males at 16000 ppm |
| 870.4300 Combined Chronic Toxicity/Carcinogenicity (Sprague Dawley rat) | 42980901 (1993) 43335101 (1994) acceptable/guideline 0, 100, 1000, or 2000 ppm Males 0, 4.23, 43.2, or 88.5 mg/kg/day Females 0, 5.93, 62.7, or 125.3 mg/kg/day | See above 870.4200a |
| 870.4200a Carcinogenicity (Osborne-Mendel rats) | 00117443 () Acceptable/non-guideline 0, 4250, or 8500 ppm for 80 weeks | Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. . High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid. Study deficiencies (CPRC, 1988); evidence equivocal. |
| Gene Mutation 870.5100 *Salmonella/Escherichia* bacterial reverse mutation assay | 41222508 (1989) Acceptable/ Guideline 66.7, 100, 333, 667, 1000, or 3300 µg/plate in the presence of or 10, 33.3, 66.7, 100, 333, or 667 µg/plate absence of mammalian metabolic activation (S9-mix) | Strains TA98, TA100, TA1535, TA1537, and TA 1538 of *S. typhimurium* were exposed to TCVP from concentrations of 66.7 to 3300 µg/plate in the presence and 10-667 µg/plate absence of mammalian metabolic activation (S9-mix).<br>There was no evidence of induced mutant colonies over background. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| *In vitro* mammalian cytogenetics 870.5375 Chinese hamster ovary cells | 41312901 (1989) Acceptable/ Guideline Concentrations of 22.9, 44.9, 59.9, 79.8, or 99.8 µg/mL without S9; 12.5, 25, 37,6, or 75.1 µg/mL in the presence of S9-mix. | Positive for inducing chromosomal aberrations at 59.9, 79.8 and 99.8 µg/mL in absence of metabolic activation, but negative at 29.9 or 44.9 µg/mL in absence of metabolic activation.<br>Negative for inducing chromosomal aberrations at 12.5, 25, 37.6, or 75.1 µg/mL in the presence of rat S9 metabolic activation. |
| Unscheduled DNA Synthesis 870.5550 in mammalian cells in culture | 42156401 (1992) Acceptable/ Guideline Doses of 5, 7.5, 10, 15, 20, 23, 25, 27, 30, 35, or 40 µg/mL of TCVP. | Concentrations of 35 and 40 µg/mL were lethal. Results were negative. |
| 870.6100 Acute and 28-Day Delayed Neurotoxicity (Domestic hen) | 41905901 (1990) Acceptable/guide line 2500 mg/kg x 2 (21 days apart) | Does not cause delayed neurotoxicity; 4/15 died. |
| 870.6200a Acute Neurotoxicity Screening Battery (Sprague-Dawley Crl:CD®BR rats) | 42912501 (1993) Acceptable/guide line 0, 65, 325, or 650 mg/kg (gavage) | NOAEL = 65 mg/kg<br>LOAEL = 325 mg/kg, based on transient neurotoxic effects in both sexes consistent with cholinesterase inhibition. No neuropathological effects.<br><br>*Cholinesterase activity was not monitored in the study.* |
| 870.6200b Subchronic Neurotoxicity Screening Battery (Crl:CD® BR rats) | 43294101 (1994) Acceptable/guide line 0, 200, 1000, or 5000 ppm (diet) (0, 100, 500, or 250 mg/kg/day; standard conversion) | NOAEL = 5000 ppm (250 mg/kg/day); HDT<br>LOAEL = not identified.<br><br>*Cholinesterase activity was not monitored in the study.* |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.6300 Developmental Neurotoxicity (Crl: CD® (SD)IGS BR VAF/Plus® rats) | 46660601 (2005) acceptable/guideline 0, 10, 50, or 200 mg/kg/day GD 6 –LD 6 (gavage) 46791401 (2006) +control data | **Maternal** NOAEL = 200 mg/kg/day<br>LOAEL = not identified.<br>**Offspring** NOAEL = 50 mg/kg/day<br>LOAEL = 200 mg/kg/day, based on deceased body weight, body weight gain, several morphometric linear brain measurements in both sexes, and decreased absolute brain weight in males on PND 70<br>*Cholinesterase activity was not monitored in the study.* |
| 870.7485 Metabolism and Pharmacokinetics (Sprague-Dawley CD rat) | MRID 41988401 (1991) Acceptable/guideline 5 mg/kg [single and repeat (14 days)] and 250 mg/kg (single) | Most of radioactivity recovered in urine (46%-60%) and feces (38%-56%) within 48 hours post dose; major metabolite in urine was trichloromandelic acid (18%-26%); major metabolite in feces was trichlorophenylethanol (>13%).<br>Since the oral LD50 for female rats is lower than the male LD50, it is noteworthy that males of all groups excreted more total label as trichloromandelic acid, a more completely metabolized form of TCVP; high-dose females tended to excrete more of the label as desmethyl TCVP (with the phosphate group still attached to the remainder of the molecule), a compound that could be derived from TCVP with only a single metabolic step. |
| 870.7600 Dermal Penetration (Sprague Dawley CD rats) | MRID 42111501 (1991) MRID 41862401 (1991) Acceptable/Guideline 0, 0.01, 0.1, 1, or 5 mg/cm$^2$ for exposures of 0.5, 1, 2, 4, and 10 hours and 10 hour wash with 72 hour exposure | Absorbed dose following 0.01 mg/cm$^2$ dose is 9.57% following 10-hour exposure. |
| 870.7800 Immunotoxicity (Crl:CD-1(ICR) female mouse) | 48794701 (2012) acceptable/guideline 0, 75, 300, 1200 mg/kg/day | Systemic NOAEL = 1200 mg/kg/day,<br>Systemic LOAEL = not identified.<br>Immunotoxicity NOAEL = 1200 mg/kg/day.<br>Immunotoxicity LOAEL = not identified. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special study Comparative cholinesterase<br><br>*gestational CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus rats) | MRID 48291101 (2010) Acceptable/non-guideline<br>1% aqueous (w/v) methylcellulose<br>0, 75, 150, 300 mg/kg/day<br>GD 6-21 (gavage) | The main purpose of this study was to determine whether there is differential sensitivity between dams and fetuses with respect to cholinesterase inhibition following oral exposure to TCVP.<br>***RBC ChE***: Neither the dams nor the fetuses demonstrated RBC ChE inhibition at dose levels where RBC ChE inhibition (ChEI) would be expected. The repeat dosing study (2012, 48773401) conducted in the same laboratory in the same strain of rat clearly demonstrated RBC ChE inhibition at 50 and 200 mg/kg/day in female rats. In the gestational/fetal study, RBC results in the dams were ↓5.1%, ↓15%, and ↓3% RBC ChEI, with increasing dose. The fetal RBC data were of little value because only one or two fetal samples were available for the control, low, and high dose groups and no sample was available for the mid dose group. *There was no way to compare adult and fetal RBC ChE.*activity<br>***Brain ChE.*** Brain ChE inhibition was dose dependent in dams (↓31%, ↓44% and ↓67% with increasing dose). Fetal brain ChE values (↓20%, ↓20.9% and ↓20.8%, with increasing dose) showed no dose-response and are questionable. However, the data suggest that the fetal brain ChE is not more sensitive to inhibition by TCVP than the dams.<br>***Plasma ChE***. Plasma ChE inhibition in dams was dose dependent ↓62%, ↓71% and ↓77%, with increasing dose). Fetal plasma ChE values were ↓22%, ↓18.5% and ↓20.8%, with increasing dose. The lack of a dose response raises questions as to whether these lower values are actually inhibition. However, the data do not indicate that the fetuses are more sensitive than the dams.<br><br>***Classification:*** This *in vivo* comparative ChE study is classified as **Acceptable/non-guideline**. The inability of the laboratory to detect RBC ChE in the dams and the flat dose response curves for the brain ChE in both pups and adults confounds the interpretation of the study. However, no additional gestational CCA study is being requested at this time because there is no indication that the fetuses were more sensitive than the dams. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special studies Comparative cholinesterase<br><br>*Acute CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain rat) | MRID 48294601 (2010) Acceptable/non-guideline<br>Single gavage dose (1% aqueous methylcellulose) young adult, PND 11, PND 21 0, 75, 150 or 300 mg/kg | The main purpose of this study was to determine whether there is differential sensitivity among the PND11, PND21 and adults with respect to cholinesterase inhibition following exposure to TCVP.<br>Overall, there is little confidence in the ChE data mainly because of the lack of clear dose and temporal responses. The number of samples in many cases was inadequate due to sample loss (no sample available, 1, 2, or 3 samples). Also, duplicate samples that did not replicate contributed to the low number of samples available for a meaningful assessment. Brain ChE assessment also appeared to be affected by the low number of samples. The results for all three enzyme sources indicated that there was inhibition at all doses but there was poor dose response with the degree of apparent inhibition at the higher doses often less that at the low dose of 75 mg/kg/day. There was also a lack of temporal concordance with high apparent inhibition at one time, a much lower degree at the following time point, and back to the higher level at the next time point. Further, there was more or similar apparent inhibition at the low dose of 75mg/kg in this acute study than there was in the repeat dosing study (2012, MRID 48773401, eleven daily doses) at 200 mg/kg/day and in the gestational study (2010, MRID 48291101, fifteen daily doses). It is noted that the repeat dosing study indicated that there was no increase in sensitivity of the pups relative to the adults with regard to ChEI by TCVP. However, in this acute study, there were several comparisons among the PND11, PND21 and adults that suggested the pups were more sensitive. Although there is little confidence in the ChEI data in this study, no additional acute CCA study is being requested at this time.<br>***Benchmark Dose (BMD) modeling.*** BMD modeling was performed but could not be done with the RBC data or for the PND11 brain data because of too few samples and/or the data would not otherwise fit the models. BMD modeling for the brain ChE data (3-hour time point) indicated that for males, the adults were slightly more sensitive than the PND 21 pups but the females were considered similar with respect to the $BMD_{10}$ and $BMDL_{10}$.<br><br>**TCVP/Study** \| **Sex/Age** \| **Compartment** \| **BMD Results** (mg/kg/day) \| **$BMD_{10}$** \| **$BMDL_{10}$**<br>MRID 48294601 Acute CCA \| Adult male \| Brain \| 6.76716 \| 5.02249<br>MRID 48294601 Acute CCA \| Adult female \| Brain \| 11.2932 \| 4.55107<br>MRID 48294601 Acute CCA \| Male pup PND 21 \| RBC \| 16.8647 \| 9.71265<br>MRID 48294601 Acute CCA \| Female pup PND 21 \| Brain \| 9.80073 \| 4.6942<br>MRID 48294601 Acute CCA \| Male pup PND 21 \| Brain \| 11.246 \| 6.76389<br><br>This study is classified as **Acceptable/Non-Guideline.** There is too much variability in the ChE data to make meaningful comparisons for sensitivity for RBC and brain ChE inhibition. Although there is little confidence in the ChEI data in this study, no additional acute CCA study is being requested at this time. **UPDATE: another acute CCA study report was identified (MRID 48773401a); see below.** |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special studies Comparative cholinesterase acute CCA<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain | 48773401a (2012) Acceptable/Non-guideline. 0, 5, 10, 50 or 200 mg/kg/day single gavage dose (1% aqueous methylcellulose; 10 mL/kg) young adult, PND 11 pups, PND 21 pups | The NOAEL for adult rats (both sexes) for RBC and brain cholinesterase inhibition following an acute oral dose was not determined. The LOAEL for adult rats is 10 mg/kg.<br><br>The NOAEL for PND 21 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg.<br><br>The NOAEL for PND 11 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg. |

| TCVP/Study | Sex/Age | Compartment | BMD Results (mg/kg) | |
|---|---|---|---|---|
| | | | $BMD_{10}$ | $BMDL_{10}$ |
| MRID 48773401a Acute CCA | Male PND11 | Brain | 5.1 | 4.5 |
| | Female PND11 | Brain | 5.9 | 4.8 |
| MRID 48773401a Acute CCA | Male PND11 | RBC | 5.0 | 4.1 |
| | Female PND11 | RBC | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | Male PND21 | Brain | 3.5 | 3.2 |
| | Female PND21 | Brain | 5.3 | 3.7 |
| MRID 48773401a Acute CCA | Male PND21 | RBC | 3.2 | 2.8 |
| | Female PND21 | RBC | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Male Adult | Brain | 7.4 | 5.6 |
| | Female Adult | Brain | 11.6 | 9.8 |
| MRID 48773401a Acute CCA | Male Adult | RBC | 6.5 | 3.6 |
| | Female Adult | RBC | 14.9 | 11.2 |

| | | |
|---|---|---|
| Special studies Comparative cholinesterase<br><br>*repeat CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain rat) | 48773401 (2012) Acceptable/Non-guideline.<br>0, 5, 10, 50 or 200 mg/kg/day for both ages. | The main purpose of this study was to determine whether there is differential sensitivity between young adults and PND 11 pups with respect to cholinesterase inhibition following repeat oral exposure (11 doses) to TCVP.<br><br>Table 1 shows the adult ChEI data (3 hours after last dose) and Table 2 shows the pup ChEI data. There was a dose-related reduction in RBC and brain cholinesterase activity in both sexes and both age groups |

**Table 1. Inhibition (%) of RBC and Brain ChE Activity in Adult Rats (repeat)**

| Dose (mg/kg/day) | Males | Females |
|---|---|---|
| **RBC** | | |
| 5 | 12% | 8% |
| 10 | 13%* | 8.7% |
| 50 | 30%** | 40%** |
| 200 | 36%** | 62%** |
| **Brain** | | |
| 5 | 2% | - |
| 10 | 7% | 12%* |
| 50 | 14.9%** | 42%** |
| 200 | 17.8%** | 57%** |

**Table 2. Inhibition (%) of RBC and Brain ChE Activity in Pups (repeat)**

| Dose (mg/kg/day) | Males | Females |
|---|---|---|
| **RBC** | | |
| 5 | 2% | - |
| 10 | 2% | - |
| 50 | 33%** | 19%** |
| 200 | 60%** | 62% |
| **Brain** | | |
| 5 | 4% | 4% |
| 10 | 6% | 6% |
| 50 | 16%** | 18.7%** |
| 200 | 46%** | 45%** |

RBC ChE inhibition. At 50 mg/kg/day, both male pups and male adults had similar levels of inhibition (30% to 33%), whereas at 200 mg/kg/day, the male pups were inhibited to ≈60% compared to 36% in the male adult rats. At 50 mg/kg/day, adult females demonstrated more inhibition (≈40%) than the female pups (19%) but at 200 mg/kg/day, both female pups and female adults had ~62% inhibition.
Brain ChE inhibition. Adult females displayed greater brain ChE inhibition at all dose levels than the adult males, whereas a similar magnitude of brain ChE inhibition was observed in male and female pups. Adult females displayed brain ChE inhibition at all dose levels.
A benchmark dose analysis of the cholinesterase data (RBC and brain) was performed that provides both the $BMD_{10}$ and $BMDL_{10}$ of adults and PND11 pups.

**$BMD_{10}$s and $BMDL_{10}$s for Adult Rat and PND 11 Pup Cholinesterase**

| | RBC $BMD_{10}$ | RBC $BMDL_{10}$ | Brain $BMD_{10}$ | Brain $BMDL_{10}$ |
|---|---|---|---|---|
| Adult ♂ | 7.7178 | 3.5942 | 33.803 | 24.4489 |
| Adult ♀ | 8.6762 | 6.1335 | 7.1764 | 5.4980 |
| PND 11 ♂ | 20.4688 | 15.9719 | 33.4825 | 26.5707 |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | | | | | |
|---|---|---|---|---|---|---|
| Guideline No./ Study Type | MRID No. (year)/ Classification /Doses | Results | | | | |
| | | PND 11 ♂ | 20.5608 | 13.1692 | 24.2224 | 18.9412 |
| | | *Overall conclusion.* The main objective of this study was to determine if the pups are more sensitive than the adults to the inhibitory potential of TCVP. Based on assignment of the NOAEL and LOAEL and the BMD modeling, there was no demonstration for increased sensitivity of the pups relative to the adults for either RBC or brain ChE. It is noted, however, that the magnitude of the high dose male pup brain and RBC ChE inhibition is greater than that in the adult males, but the significance is not established. | | | | |

## A.3 Hazard Identification and Endpoint Selection

### A.3.1 Acute Dietary Reference Dose (aRfD) – All Populations

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No**.: 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Data from the young rat from the acute CCA study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations. The study provides the lowest POD following a single dose. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) results in an aPAD of 0.0028 mg/kg/day; the (FQPA) factor may be excluded for the sub-population of adults 50-99 (aPAD of 0.028 mg/kg/day).

### A.3.2 Steady State Reference Dose (ssRfD) –All Populations

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No.:** 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg/day associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Although the steady state dietary endpoint was selected from an acute dose comparative cholinesterase study, the duration of this study is considered appropriate for this exposure scenario since AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose. A longer-term exposure does not result in a lower POD, as evidenced by the larger $BMD_{10}$s found for the repeat dose CCA data.

The point of departure is protective of any exposure duration longer than 21-days, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady state and occurs following one exposure to TCVP. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) results in an ssPAD of 0.0028 mg/kg/day; the (FQPA) factor may be excluded for the sub-population of adults 50-99 (ssPAD of 0.028 mg/kg/day).

### A.3.4 Incidental Oral Exposure (Steady-State)

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No**.: 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Data from the young rat from the acute CCA study are appropriate for the incidental oral assessment since the AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose, and the endpoint is the most sensitive adverse response in all populations. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) is appropriate for incidental oral exposures.

### A.3.6 Dermal Exposure

There is no potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day, and there is no concern for quantitative susceptibility.

### A.3.7 Inhalation Exposure (Steady State)

**Study Selected:** 28-day Inhalation Toxicity Study
**MRID No**.: 48803501
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 0.02 mg/L/day associated with RBC ChE inhibition in both sexes, following inhalation exposure, was selected as a suitable POD for assessing the potential risk associated with inhalation exposure (single day and steady-state). The corresponding $BMD_{10}$ was 0.12 mg/L/day.

**Comments about Study/Endpoint/Uncertainty Factors:** A route-specific, 28-day inhalation toxicity study was used for the steady-state inhalation assessment. Using the Agency's Reference concentration (RfC) methodology, human equivalent concentrations (HECs) and Human

Equivalent Doses (HEDs) was calculated for residential and occupational handlers. Since the inhalation POD is based on a route-specific toxicity study, no absorption factor is necessary to estimate exposure. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

A total uncertainty factor of 30X is appropriate for inhalation exposures [3X for interspecies extrapolation, 10X for intraspecies variation] for adult males and females 49+. The FQPA safety factor (10X) will be retained for infants, children, youths, and women of child-bearing age for all exposure scenarios to account for uncertainties introduced by the lack of sufficient data to quantify potential neurodevelopmental effects observed in epidemiology data on the OP, chlorpyrifos.

## A.4 Executive Summaries

### A.4.1 Subchronic Toxicity

#### 870.3100 90-Day Oral Toxicity – Rat

In a subchronic oral toxicity study (MRID 43371201), tetrachlorvinphos (TCVP; 99% a.i.; Batch KMJ 012) was given to Sprague Dawley rats (10/sex/group) in the diet at doses of 0, 100, 2000, or 5000 ppm (0, 6.7, 142, and 375 mg/kg/day for males; 0, 10.0, 197, and 467 mg/kg/day for females) for 13 weeks.

Survival was not adversely affected in either sex, and there were no clinical signs of toxicity. There were no effects on body weight in the females, but decreased body weight (7%-12%) was observed in males at 5000 ppm throughout the study.

Red blood cell (RBC) cholinesterase (ChE) inhibition was observed in males at 2000 ppm (30%) and 5000 ppm (72%) and in females at 2000 ppm (79%) and 5000 ppm (91%). A noteworthy finding was that 2 rats/sex at 5000 ppm had no measurable RBC ChE activity at 13 weeks. Brain cholinesterase inhibition was observed in females at all dose levels (12%, 14%, 24%, with increasing dose), but statistical significance was not attained at any dose level. Brain cholinesterase inhibition was not observed in males.

Liver weight was increased in females at 2000 ppm (22% when adjusted for body weight) and at 5000 ppm 22%-28%, actual and adjusted). Males displayed an increase in adjusted liver weight (8% and 19% at 2000 ppm and 5000 ppm, respectively). Increased kidney weights were observed in males at 5000 ppm (18% adjusted for body weight), and increased adrenal weights (actual/adjusted) were observed in females at 2000 ppm (20%/28%) and 5000 ppm (28%/32%). There was a dose-related increase in the incidence and severity of bilateral basophilic tubules of the kidneys in males and in the incidence of cellular alteration (fat deposition) in the adrenal cortex of females at 2000 ppm (7/10) and 5000 ppm (9/10). All females at 2000 ppm and 5000 ppm displayed centrilobular hepatocellular hypertrophy, with the severity increasing with dose. In males, the incidence of hepatocellular hypertrophy was significantly increased at 2000 ppm (8/10),

with 2 displaying general cell enlargement, whereas only 1/10 males at 5000 ppm displayed hepatocellular hypertrophy and 7/10 displayed general cell enlargement in the liver. There was a dose-related increase in the incidence of thyroid follicular cell hypertrophy in both sexes.

The NOAEL is 6.7 mg/kg/day, based on RBC ChEI in both sexes (males 30%*; females 79%**), bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females, higher adjusted liver weights (both sexes), higher adjusted adrenal weights in females, and thyroid follicular cell hypertrophy in both sexes at the LOAEL of 142 mg/kg/day. At 467 mg/kg/day, decreased body weight was observed throughout the study in males (7%- 12%), with the magnitude of the deficit increasing over time, females had a 24% brain cholinesterase activity inhibition, although statistical significance was not attained (females 12%, 14%, 24% brain ChEI with increasing dose; males 1% at HDT), and both sexes displayed RBC ChEI (males 72%; females 91%).

This study is classified as Acceptable/Guideline, and it satisfies the guideline requirement (OCSPP 870.3100; OECD 408) for a subchronic oral toxicity study in the rat.

**Single Day and 21-Day Oral Toxicity – Rat**

In a 21-day oral toxicity study (MRID 45570601), tetrachlorvinphos (99.1% a.i., lot #801066) was administered to 18 Crl:CD®(SD)IGS BR rats/sex/dose by gavage at dose levels of 0, 8, 12, 20, or 50 mg/kg/day. Seven or eight animals/sex/group were ***sacrificed approximately 3.5 hours following the first dose*** (time to peak effect); the remaining 10/sex/group were killed after an additional 21 days of dosing. Blood samples were taken for plasma and RBC cholinesterase (ChE) determinations approximately one week prior to study initiation, 3.5 hours following dosing on the first day (day 0), on study days 1, 7, and 14, and at study termination (day 21). Whole brain ChE levels were measured after sacrifice on days 0 and 21.

No treatment-related clinical signs of toxicity or deaths were observed in any animal during daily observations or 1 hour post-dosing. Body weights were similar between the treated and control groups throughout the study.

Dose-related inhibition of ChE activity was observed following both acute and repeated exposures. Inhibition in females occurred at a lower dose than in males. Following a single dose of 50 mg/kg, inhibition of plasma ChE activities (63-67%) relative to concurrent controls were observed in males and females. Also significant inhibition (37-46%) of plasma ChE activities were observed in males and females at 20 mg/kg and in females at 12 mg/kg. However, the LOAEL for plasma ChE inhibition was 8 mg/kg based on inhibition of plasma ChE activity relative to pretest values in males. The NOAEL for plasma ChE inhibition was not established. Significant inhibition (37-46%) of RBC ChE activities from both sexes were observed at 50 mg/kg only. Significant inhibition of whole brain ChE was observed n males at 50 mg/kg (54%) and 20 mg/kg (22%) and in females at 50 mg/kg (23%).

Following repeated exposure, plasma ChE activity in the 20- and 50-mg/kg/day males was similar to the concurrent control levels at each time point with the exception of the high-dose males on day 1 (25% inhibition). However in females, plasma ChE activity was significantly inhibited by 26-30% in the 8-mg/kg/day group beginning on day 14 and by 23-67% in the 12-, 20- and 50-mg/kg/day groups beginning on day 1. Inhibition of RBC ChE levels in 50-mg/kg/day males and females was transient with a maximum inhibition at day 7 (44% and 57%, respectively) followed by modest recovery in males and slight recovery in females. Whole brain ChE activity in males was not affected by repeated exposure. In contrast, significant inhibition of brain ChE activities were observed in the 50 mg/kg/day (36%) and 20 mg/kg/day (16%) females.

**Following both a single and 21-day repeated dose of tetrachlorvinphos, the LOAEL for brain ChE inhibition was 20 mg/kg, based on inhibition of brain ChE activity in males with a NOAEL of 12 mg/kg.**

**Following a single dose of tetrachlorvinphos, the LOAEL for erythrocyte ChE inhibition was 50 mg/kg, based on inhibition of erythrocyte ChE activity with a NOAEL of 20 mg/kg.** Because reproducibility of ChE activity of the rat RBC samples was poor and the standard deviations were large for all groups, the RBC ChE inhibition measurements in the 21-day toxicity study were judged to be unreliable. Therefore, the HIARC (TXR# 0050548; dated March 7, 2002) concluded not to use RBC ChE data from this 21-day study due to lack of confidence in the results.

**Following single and repeated exposure to tetrachlorvinphos, the LOAEL for plasma ChE inhibition was 8 mg/kg, based on inhibition of plasma ChE activity relative to pretest values in males. The NOAEL for plasma ChE inhibition was not established.**

This study is classified as Acceptable/non-Guideline, and it does not satisfy any guideline requirement.

**870.3150 90-Day Oral Toxicity - Dog**

No subchronic study.

**870.3200 21/28-Day Dermal Toxicity - Rat**

In a repeat dose dermal toxicity study (MRID 41342001), male and female Crl:CD BR rats (5/sex/dose) received dermal applications of 0, 10, 100, or 1000 mg/kg/day Rabon Technical (TCVP; 99% a.i.; ) moistened with deionized water for 6 hours/day, 5 days/week for a total of 15 treatments over a 21-day period.

Rabon Technical did not induce significant dermal effects at dose levels up to and including 1000 mg/kg/day. Treatment caused a statistically significant decrease in plasma cholinesterase activity in females at 1000 mg/kg/day. Plasma cholinesterase was also lower than control values for males at the mid and high doses and females at the mid dose; these differences were not statistically significant. TCVP did not result in brain or RBC AChE inhibition, and there were no adverse effects on mortality, body weight, food consumption, hematology, clinical chemistry, organ

weights, or gross and histopathology. The NOAEL is established at 1000 mg/kg/day (the limit dose), since plasma cholinesterase inhibition is not considered a relevant adverse endpoint.

This study is classified as Acceptable/non-Guideline. The study does not satisfy the guideline requirement (OCSPP 870.3200) for a repeat dose dermal toxicity study since an inadequate number of animals per dose were tested; however, the study is adequate for the determination that a dermal risk assessment is not required for TCVP.

### 870.3465 Subchronic Inhalation – Rat

In a nose-only inhalation toxicity study (MRID 48803501), tetrachlorvinphos (TCVP; Lot No. TX 100113; 100% purity) aerosol was administered to male and female Sprague-Dawley rats (10/sex/concentration) for 6 hours/day, 5 days/week for 3 weeks at exposure concentrations of 0, 0.05, 0.5, or 1.0 mg/L. During the final week of exposure (week 4), the animals were exposed for 7 days. An additional 10 rats/sex/concentration were included in the control and high dose groups and sacrificed 14 days after completion of the 28-day exposure period to determine the reversibility of any effects observed. Actual exposure concentrations as measured by HPLC were 100%, 100%, and101% of target values. The mass median aerodynamic diameters (MMADs) ± geometric standard deviations (GSD) were 2.57 µm ±3.785, 4.51 µm ±3.541, and 4.27 µm ±3.343 for the low-, mid- and high concentrations, respectively.

There were no treatment-related deaths. Treatment-related reduced body weights (↓7%* and ↓8%**) and body weight gains (↓27%** and ↓34%***) were observed in males from the mid- and high exposure groups, respectively. The body weight difference persisted through the recovery period in the high-exposure (↓12%) male recovery group, but the weight gain during those 2 weeks was slightly higher (5%) relative to the control group. Bodyweight was comparable among the female groups throughout the study. Body weight gain was reduced in mid- (↓23%) and high (↓32%) exposure females, but body weight gain was comparable to the control during the recovery period. Food consumption was decreased throughout the study in the mid- and high male groups and during the first two weeks in the low dose male group, whereas food consumption was comparable among the female groups. There were no treatment-related findings during the ophthalmoscopic examinations. Decreased hemoglobin concentration and increased platelets were noted in high exposure concentration females, but these findings were no longer evident at the end of the 2-week recovery period. Calcium was slightly, but significantly, elevated in males at all three exposure levels, but there was no dose-response. Cholesterol was significantly elevated in females from the mid- (↑22%) and high (↑27%) exposure groups. These findings were not observed in the recovery group.

Statistically significant RBC ChE activity inhibition ($p<0.001$) was observed in females at the mid- and high exposure concentrations (35% and 30%, respectively). Statistically significant AChE and RBC ChE activity inhibition ($p<0.001$) was observed in males at the mid- and high exposure concentrations (38% and 31% for AChE, respectively; 24% and 31% for RBC ChE, respectively). Plasma acetylcholinesterase activity (58% to 70%) and plasma butyrylcholinesterase activity (66% to 87%) were decreased relative to controls at all exposure

concentrations in females. All cholinesterase activities were lower relative to controls in the male and female recovery groups, but the differences were not statistically significant.

Treatment-related gross findings were limited to discoloration and enlargement of the adrenal glands at the mid- and high exposure concentrations in males, and in females at all exposure concentrations. Diffuse adrenal cortical cell vacuolation (minimal to moderate with an exposure-related incidence) was observed in both males and females at all exposure concentrations. Minimal follicular cell hypertrophy of the thyroid gland was observed with an exposure-related incidence in both sexes at the mid- and high exposure concentrations. Minimal to mild ovarian interstitial cell vacuolation was observed with an exposure-related incidence in females at the mid- and high exposure concentrations. The findings in the thyroid and ovary were referred to as "commonly observed in this strain and age of rat," but no historical control data or literature citations were provided. In the recovery group, 2/5 males and 2/5 females at the high dose had minimal diffuse adrenal cortical cell vacuolation (0/5 incidence in recovery controls). No other treatment-related microscopic findings were observed in the recovery group.

**Based on the effects seen in this study, a systemic NOAEL in male and female Sprague-Dawley rats was not identified. The systemic LOAEL in male and female rats was 0.05 mg/L, based on diffuse adrenal cortical cell vacuolation in both sexes, enlarged adrenals in females, and increased adrenal weights in females. At 0.5 mg/L and 1.0 mg/L, in addition to the adrenal findings, there was a dose-related increase in vacuolation of the ovaries in females, an increase in squamous metaplasia of the larynx in both sexes, and an increase in follicular cell hyperplasia of the thyroids in both sexes.**

**The NOAEL for cholinesterase inhibition was 0.05 mg/L, based on an increase in RBC cholinesterase inhibition in both sexes at 0.5 mg/L/day. Brain cholinesterase activity was not monitored.**

The RBC cholinesterase data from this study have been evaluated using benchmark dose modeling techniques. The results are shown below.

| **$BMD_{10}$/$BMDL_{10}$ Results (mg/L)** | | | |
|---|---|---|---|
| **Sex/Age** | **Compartment** | **$BMD_{10}$** | **$BMDL_{10}$** |
| Female | RBC | 0.394 | 0.050 |
| Male | RBC | 0.122 | 0.022 |

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for a repeat dose inhalation toxicity study.

COMMENT: Although a no effect dose was not identified for the findings in the adrenal (LOAEL 8.7 mg/kg/day), when compared on a mg/kg/day basis to the $BMDL_{10}$ (95% lower confidence limit on the $BMD_{10}$) established for cholinesterase inhibition, the point of departure



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(POD; 1.31 mg/kg/day) used in the inhalation exposure risk assessment is protective of these adrenal findings.

### A.4.2 Prenatal Developmental Toxicity

#### 870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 40152701), tetrachlorvinphos (98.6% ai; Lot No. 10-56-0-0) was administered *via* gavage to groups of 25 Sprague-Dawley Crl:COBS®CD®(SD)BR pregnant rats/groups at dose levels of 0 (0.5% methyl cellulose), 75, 150, or 300 mg/kg/day from gestation day (GD) 6 through GD 15.

All dams survived until study termination. At 300 mg/kg/day, one dam displayed tremors from day 10 onward, and chromodacryorrhea was observed only at this dose level. Although body weights were comparable among the groups, body weight gains were significantly reduced at 300 mg/kg/day throughout the dosing period (52%), and food consumption was also reduced. The numbers of corpora lutea, implantations, resorptions, and dams with liable fetuses were comparable among the groups. The mean number of live fetuses, sex ratio, and fetal body weights were comparable among the groups.

The maternal NOAEL is 150 mg/kg/day, and the maternal LOEL is 300 mg/kg/day, based on tremors and an increased incidence of chromodacryorrhea.

The developmental NOAEL is 300 mg/kg/day, the highest dose tested. A developmental LOAEL was not determined.

The developmental toxicity study in the rat is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; 83-3a) in the rodent when combined with MRID 41828001, MRID 41967201, and MRID 42520101. NOTE: The maternal NOAEL/LOAEL differ from the original assessment due to the current policy that decreases in body weight gain without significant reduction in body weight is not considered an adverse effect.

#### 870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a prenatal developmental toxicity study (MRID 00127831), New Zealand White rabbits (#/sex/dose) were administered tetrachlorvinphos (98% a.i.; T-142-3) by gavage at doses of 0, 150, 375, or 750 mg/kg/day in 5 mL/kg carboxy methylcellulose on gestation days 6-19.

Maternal toxicity at the highest dose tested was manifested as mortality (0/18, 1/18, 1/8, 2/18), abortions (0, 1, 0, 3), and red vaginal fluid (0, 1, 1, 8) in the control, low, mid, and high-dose groups, respectively.

**The maternal NOEL is 375 mg/kg/day, and the maternal LOEL is 750 mg/kg/day.**

Developmental toxicity at the highest dose tested was manifested as an increase in early resorptions/dam (0.4, 0.5, 0.3, 1.4), with a corresponding increase in postimplantation loss (10.6%, 5.6%, 10.5%, 21.9%) and a decrease in live fetuses/dam (7.7, 7.8, 6.9, 5.8) for the control, low, mid, and high-dose groups, respectively.

**The developmental NOEL is 375 mg/kg/day, and the developmental LOEL is 750 mg/kg/day.**

This developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; 83-3b) in rabbits.

### A.4.3 Reproductive Toxicity

#### 870.3800 Reproduction and Fertility Effects - Rat

In a 2-generation reproduction study (MRID 00127831), 28 Charles River CD Crl: (SD) BR Sprague Dawley rats/sex/dose were administered tetrachlorvinphos (99% a.i.; technical Rabon) *via* the diet at doses of 0, 100, 500, or 2000 ppm (F0 males: 0, 5.2, 26, or 102 mg/kg/day/F0 females: 0, 7.3, 40, or 155 mg/kg/day; F1 males: 0, 6.7, 34, or 130 mg/kg/day/F1 females: 0, 8.3, 43, or 168 mg/kg/day). Treatment of the F0 rats began when they were approximately 6 weeks old, and after 10 weeks, they were bred to produce F1 animals. Treatment continued throughout the mating, gestation, and lactation periods, with termination of the F0 rats after weaning of their litters. The F1 rats were weaned onto the same diets as their parents, and groups of 24 rats/sex/dose were selected as the F1 generation. The F1 rats were treated for 11 weeks and then mated to produce F2 litters. Treatment also continued throughout the mating, gestation, and lactation periods. Termination of the F1 and F2 animals occurred at the time of weaning of the litters.

There was no adverse effect on survival, and no clinical signs of toxicity were observed in either generation. Body weights of the adult animals were not adversely affected in either generation. Increased adrenal weights in the F0 females at 2000 ppm were considered treatment-related, although a similar increase in adrenal weight was not observed in the F1 females or in males of either generation. Fertility indices, duration of gestation, mean number of implantation sites, number of stillborns, mean litter size, pup survival, and pup body weights were comparable among the groups in both generations.

**The parental NOAEL is 500 ppm (males 26/females 40 mg/kg/day). The parental LOAEL is 2000 ppm (males 102/females 155 mg/kg/day), based on increased adrenal weights of F0 females**.

**The offspring NOAEL is 2000 ppm (males 102/females 155 mg/kg/day). The offspring LOAEL was not identified.**

**The reproductive NOAEL is 2000 ppm (males 102/females 155 mg/kg/day). The reproductive LOAEL was not identified.**

Note: Although minimal toxicity was observed, and higher doses would have been tolerated, cholinesterase measurements were not performed in this study. Based on findings in other studies in the TCVP database, cholinesterase inhibition would have been observed in this study, if monitored, at the mid and high dose levels.

The 2-generation reproduction toxicity study in the rat is classified Acceptable/Guideline, and it satisfies the guideline requirement for a reproduction toxicity study (OCSPP 870.3800; OECD 416) in the rodent.

### A.4.4 Chronic Toxicity

#### 870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic toxicity/carcinogenicity study (MRID 42980901/43335101), groups of Sprague-Dawley rats (50/sex/group) were administered tetrachlorvinphos (99% a.i.) *via* the diet at dose levels of 0, 100, 1000, or 2000 ppm (males 0, 4.23, 43.2, or 88.5 mg TCVP/kg/day; females 0, 5.93, 62.7, or 125.3 mg TCVP/kg/day) for two years.

Survival was comparable among the groups in both sex, and there were no treatment-related clinical signs of toxicity. Body weight was comparable among the male groups, and females at the high dose displayed slightly lower body weights (8%-12%) than the controls from week 10 on (12% at 52 weeks; 8% at 104 weeks). Food consumption was comparable among the groups.

Females at 2000 ppm had significantly elevated cholesterol levels at weeks 77/78 and 104. Effects at 1000 and 2000 ppm in both sexes included an increased incidence and tendency to greater severity of diffuse lipidosis of the adrenal zona fasciculata, hypertrophy of periacinar hepatocytes, centriacinar degenerative (males only) changes of the liver, and reduced alkaline phosphatase activity.

RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **). Brain cholinesterase inhibition was observed in females at 52 and 104 weeks was 17% and 16% (not **). BMDs were not run due to lack of dose-response in both compartments.

The systemic toxicity NOAEL is 100 ppm (4.23/5.93 mg/kg/day). The systemic toxicity LOAEL is 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes).

Increased incidence of thyroid C-cell adenomas was observed in male rats at the highest dose and adrenal pheochromocytomas were observed in males.(both sexes). The LEL is 1000 ppm, based on decreased body weight in females, histological liver and adrenal changes in both sexes.



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The study is classified Acceptable/Guideline, and it satisfies the guideline requirements for a combined chronic toxicity/carcinogenicity study (OCSPP 870.4300; OECD 453), a chronic oral toxicity study (870.4100; OECD 452), and a carcinogenicity study (870.4200; OECD 451) in the rodent.

#### 870.4100b Chronic Toxicity – Dog

In a chronic oral toxicity study (MRID 42679401), tetrachlorvinphos (TCVP; 99% a.i.; Batch 01-KMJ-012) was given to outbred Beagle dogs (4/sex/group) *via* capsule at doses of 0, 6.25, 500, or 1000 mg/kg/day for 52 weeks.

Survival was not adversely affected in either sex, and there were no clinical signs of toxicity. There were no treatment-related effects on body weight or food or water consumption, and no differences in ophthalmologic, macroscopic, and microscopic findings in either sex.

Treatment-related decreases in red blood cell counts at 500 and 1000 mg/kg/day were corroborated by decreases in hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit, and increases in mean corpuscular volume. The kidney and liver weight increases at 500 and 1000 mg/kg/day in both sexes may be related to the alkaline phosphatase increases (both sexes) and cholesterol decreases (males) observed, but no histopathological correlates were evident. The decreases in urine specific gravity at 500 and 1000 mg/kg/day in both sexes may be related to the kidney weight increases at these dose levels, but histopathological correlates were not evident.

RBC and brain cholinesterase inhibition were not observed at any dose level in either sex at any time point monitored.

The systemic toxicity NOAEL is 6.25 mg/kg/day. The systemic toxicity LOAEL is 500 mg/kg/day, based on decreased red blood cell counts, hemoglobin, hematocrit, MCHC, MCV, alkaline phosphatase, urine specific gravity, and decreased liver and kidney weights.

The chronic toxicity study is classified Acceptable/Guideline, and it satisfies the guideline requirement for a chronic toxicity study (OCSPP 870.4100; OECD 452) in the non-rodent.

### A.4.5 Carcinogenicity

#### 870.4200a Carcinogenicity Study – Rat

In the combined chronic toxicity study (MRID 42980901/43335101), groups of 50 male and 50 female Charles River Sprague-Dawley rats received TCVP in their diet over a 2-year period at 0, 100, 1000 or 2000 ppm (equivalent to 0, 4, 43 and 89 mg/kg/day in males and 0, 6, 63 and 125 mg/kg/day in females, respectively). See above under 870.4100a.

There were increases in the incidences of thyroid C-cell adenomas and adrenal pheochromocytomas in male rats only. Neither of these increases were statistically significant by pairwise comparison to controls, but there was a statistically significant increasing trend for the adrenal tumors.

This study is classified as Acceptable/Guideline, and it satisfies the guideline requirements (870.4200; OECD 451] for a carcinogenicity study in the rat.

In another rat study (MRID 00117443; 1978 NCI-sponsored Gulf South study), Osborne-Mendel rats received TCVP in their diet at doses of 0, 4250, or 8500 ppm for 80 weeks, followed by 31 weeks observation.

Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid.

This study is classified Acceptable/Non-Guideline, and it does not satisfy the guideline requirement (870.4200; OECD 451) for a carcinogenicity study.

### 870.4200b Carcinogenicity – Mouse

In a carcinogenicity study (MRID 00126039), B6C3F1 mice were fed diets containing 0, 17.5, 64, 320, 1600, 8000, or 16000 ppm tetrachlorvinphos for two years in a carcinogenicity study. For systemic toxicity, the NOAEL was 1600 ppm (240 mg/kg/day) and the LOAEL was 8000 ppm (1200 mg/kg/day), based on decreased weight gain. Administration of TCVP in the diet to B6C3F1 mice resulted in statistically significant increases in hepatocellular adenomas, carcinomas and combined adenomas/carcinomas (with carcinomas predominant) in females, and in combined hepatocellular adenomas/carcinomas in males. In male mice there were also statistically significant increases in renal adenomas, carcinomas and combined adenomas/ carcinomas. The statistically significant increases in tumors noted above, all occurred only at doses of TCVP of 8000 ppm or greater, except for the combined hepatocellular adenomas/ carcinomas in female mice, which also occurred at 1600 ppm.

This study is classified as Acceptable/guideline, and it satisfies the guideline requirements (870.4200; OECD 451] for a carcinogenicity study in the mouse.

In another carcinogenicity study (MRID 00117443), B6C3F1 mice were fed diets containing 0, 8000, or 16000 ppm TCVP for 80 weeks, followed by 12 weeks observation. Increased incidences of hepatocellular carcinomas and granulomatous lesions of the liver were found in the dosed mice.

This study is classified Acceptable/Non-Guideline, and it does not satisfy the guideline requirement (870.4200; OECD 451) for a carcinogenicity study in the mouse.



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## A.4.6 Mutagenicity

| Summary of the Genotoxicity Studies for TCVP | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| **GENE MUTATION** | | | |
| 870.5100 | Bacterial Reverse Gene Mutation Assay in *Salmonella typhimurium* | 4122508 (1989)<br><br>Acceptable/guideline<br><br>0, 10-667 µg/plate -S9<br>0, 66.7-3300 µg/plate +S9 | **Negative** up to cytotoxic concentrations at the highest dose tested +/-S9 |
| **CHROMOSOME ABERRATIONS** | | | |
| 870.5375 | *In vitro* Mammalian Cell Clastogenicity Assay in Chinese hamster ovary (CHO) cells | 41312901 (1989)<br><br>Acceptable/guideline<br><br>0, 29.9, 44.9, 59.9, 79.8, 99.8 µg/mL -S9 (20-hr cell harvest)<br>0, 12.5, 25, 37.6, 75.1 µg/mL, +S9 (10-hr cell harvest) | **Positive** Significant & dose-related increases in chromosome aberrations in the absence of S9 only after a prolonged exposure due to severe mitotic delay, unhealthy monolayers and reduced mitotic cells at 59.9 & 79.8 µg/mL. Major aberrations: chromatid & chromosome breaks<br>NOTE: Increases in chromosome aberrations were accompanied by marked increases in chromatid & chromosome gaps.<br><br>**Negative** with S9 activation up to a precipitating (≥676 µg/mL) & cytotoxic (2030 µg/mL) concentrations |
| | *In vitro* Mammalian Cell Clastogenicity Assay in Mouse spleen cells | Amer & Aly (1992)<br><br>Acceptable/nonguideline<br>0.25, 0.5, 1.0, 2.0 µg/mL (4-hr treatment) | **Chromosome aberrations**<br>**Positive:** Significant & dose-related increases in chromosome aberrations (minus gaps) at ≥0.5 µg/mL Major aberrations: chromatid & chromosome fragments<br>NOTE: Increases in chromosome aberrations were accompanied by marked increases in chromatid & chromosome gaps.<br><br>**Sister Chromatid Exchange (SCE)**<br>**Positive:** Significant & dose-related increases in SCE induction at ≥0.5 µg/mL |

| Summary of the Genotoxicity Studies for TCVP | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Micronucleus Assay in Bone Marrow Cells of the Mouse | Amer & Aly (1992)<br><br>**Oral:** 0, 3000 & 6000 ppm dietary administration daily for 14 consecutive days or 10 weeks<br>**Ip injection**: 0, 50 & 100 mg/kg weekly for 2 weeks<br>**Dermal:** 0, 1350 mg/kg 4 treatments | **ORAL:** S↑ % PCEs at 3000 & 6000 ppm after 10 weeks at 24 hours & 7 & 14 days post-treatment but **S↑% MPCEs only 6000-ppm group at 24 hours & 7 days post-treatment**<br><br>**IP INJECTION**:<br><br>**<u>50 mg/kg</u>: S↑ % MPCEs at 24 hr. post-treatment (Double injection only); % PCEs not reported.**<br><br>**<u>100 mg/kg</u> (single injection): S↑ % PCEs at 24 hr. post-treatment only.**<br><br>**<u>100 mg/kg</u> (double injection): S↑ % PCEs at 24 hr. post-treatment**<br>**S↑ % MPCEs at 24 hr. post-treatment only.**<br><br>**DERMAL:** S↑ % PCEs at 24 hr. post-treatment 1350 mg/kg (4 applications) only; no increase in MPCEs |
| **OTHER MUTAGENIC MECHANISMS** | | | |
| 870.5550 | *In vitro* unscheduled DNA synthesis (UDS) in primary rat hepatocytes | 42156401 (1992)<br><br>Acceptable/guideline<br><br>0, 10-40 µg/mL (9 doses) | **Negative**<br>Cytotoxicity was observed as follows: 35 & 40 µg/mL -lethal<br>23-30 µg/mL (moderate to high cytotoxicity)<br>15 & 20 µg/mL (slight cytotoxicity)<br>10 µg/mL (non-cytotoxic) |
| | DNA adduct formation<br>Swiss male mice<br>liver. | Zayed et al., 1983)<br>25, 50 and 100 mg/kg i.p. injection | **Positive**<br>Fraction of total applied dose associated with 7-methyl guanine was estimated to be $9x10^{-5}$ and $39x10^{-5}$ in DNA and RNA, respectively |

The relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[41].

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[41] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

## A.4.7 Neurotoxicity

### 870.6100b Delayed Neurotoxicity – Hen

In an acute delayed neurotoxicity study in hens (MRID 41905901), technical Rabon (tetrachlorvinphos; Lot # 01-KMJ-012; 99% a.i.), was administered twice orally (Mazola corn oil) to hens at 2500 mg/kg, with an intervening 21-day period (total dose 5000 mg/kg).

There was sufficient evidence of acute toxicity, including mortality (4/15), to establish that the test material was administered at a sufficiently high dose. TCVP did not result in delayed neurotoxicity, as evidenced both by in-life observations and microscopic examination of spinal cord tissue from three levels. The minimum myelin degeneration seen in 2 hens was consistent with the normal background incidence for this finding in this type of study. The positive control material (tri-0-tolyl- phosphate, TOTP) at 1000 mg/kg elicited the appropriate response.

This study is classified **as Acceptable/Guideline** and it satisfies the guideline requirement for a delayed neurotoxicity study in the hen (870.6100).

### 870.6200a Acute Neurotoxicity Screening Battery – Rat

In an acute neurotoxicity study (MRID 42912501), tetrachlorvinphos (99% a.i.; Lot #: 01-KMJ-012) was administered *via* gavage (10 mL/kg; in corn oil) to non-fasted Sprague-Dawley Crl:CD®BR rats (12/sex/dose) at doses of 0, 65, 325, or 650 mg/kg. All rats were evaluated in functional observational batteries and motor function observations on days 0, 7, and 14.

Transient neurotoxic effects were observed in both sexes on day 0 at the mid- and high-dose levels. These effects were consistent with cholinesterase inhibition. At 650 mg/kg, the predominant clinical signs observed in both sexes on the day following dosing consisted of gait alterations (prostration, rocking, lurching, and swaying when ambulatory; walked on tiptoes), constricted pupils, tremors (fore- and hindlimb), cool body to the touch, yellow material on various body surfaces, red material on forelimbs, around eyes, nose, and mouth, and/or increased defecation. Several of these findings were noted in a limited number of rats (mainly females) on days 2, 3, 4, and/or 5. At 325 mg/kg, one female showed gait alterations and one male and 3 females had constricted pupils on day 1. The neuropathologic examination gave no indication of any dose-related permanent effects on the brain or in the peripheral or central nervous tissues, consistent with the lack of permanent changes in muscular coordination and/or behavior.

The NOAEL is 65 mg/kg, and the LOAEL is 325 mg/kg, based on transient neurotoxic effects in both sexes on day 0.

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for an acute neurotoxicity study in rats (OPPTS 870.6200, OECD 424).

### 870.6200b Subchronic Neurotoxicity Screening Battery - Rat

In a subchronic neurotoxicity study (MRID 43294101), tetrachlorvinphos (99% a.i.; Lot #01-KMJ-012) was administered via the diet to 10 Sprague-Dawley Crl:CD®BR rats for 90 days at dose levels of 0, 200, 1000, or 5000 ppm. A Functional Operational battery (FOB) and motor activity were assessed at weeks -1, 0, 3, 7, and 12.

There were no deaths or clinical signs of toxicity. There were no measurement of cholinesterase activity, but cholinergic signs were not observed. Decreased body weight was observed throughout the study in males at 5000 ppm (8%-9%) and in females at 2000 ppm (8%-10%) and 5000 ppm (7%-13%). There were no indications of any dose-related effects during the home-cage, handling, open-field, sensory or neuromuscular observations. There were no significant dose-related differences between groups involving group mean motor activity counts. Brain weights and brain measurements (weight and morphometric) were comparable among the groups for both sexes, and there were no differences in histomorphological neurology findings between the control and 5000 ppm groups.

The NOAEL is 5000 ppm (250 mg/kg/day; standard conversion). The LOAEL was not identified.

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for a subchronic neurotoxicity study in rats (OPPTS 870.6200, OECD 424).

### 870.6300 Developmental Neurotoxicity - Rat

In a developmental neurotoxicity study (MRID 46660601), tetrachlorvinphos (99.6% a.i.; Lot #: NJ250RB08) in aqueous 1% (w/v) methylcellulose was administered via gavage (10 mL/kg) to pregnant Sprague-Dawley rats (25/dose) from gestation day (GD) 6 to lactation day (LD) 6 at doses of 0, 10, 50, or 200 mg/kg/day. Additionally, the $F_1$ pups were similarly dosed on postnatal days (PNDs) 7-21. Dams were allowed to deliver naturally and were sacrificed on LD 21. On PND 4, litters were standardized to 10 pups/litter; the remaining offspring and dams were sacrificed and subjected to a gross necropsy. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following subsets: Subset 1, PND 21 brain weights and neurohistological evaluations; Subset 2, water maze and passive avoidance test; Subset 3, motor activity and auditory startle habituation; Subset 4, terminal brain weights and neurohistological evaluations; and Subset 5, standardize litter size to ten pups (5 male and 5 female) per litter on PND 4-21.

In dams, there were no treatment-related effects on mortality, clinical signs, body weight, body weight gain, feed consumption, FOB, or gross pathology. No treatment-related effects on reproductive parameters were observed. **The maternal LOAEL was not observed. The maternal NOAEL was 200 mg/kg/day (HDT).**

In offspring, there were no treatment-related effects on viability, litter observations, clinical signs, body weight, food consumption, FOB, motor activity, acoustic startle habituation, learning and memory (passive avoidance and water maze), gross pathology, or histopathology parameters.

At 200 mg/kg/day, decreases ($p \leq 0.05$) in body weight were noted in the males (↓5-8%) on PNDs 15 and 16 (pre-weaning) and PND 22 (post-weaning) and in the females (↓6%) on PND 29 (post-weaning). Body weight gains were decreased ($p \leq 0.05$) during pre-weaning at several intervals in the males (↓12-28%) and females (↓13-26%). Decreases ($p \leq 0.05$) in body weight gains during post-weaning were observed in the males on PNDs 21-22 (↓36%) and in the females on PNDs 21-22 and 22-29 (↓7-28%). Absolute brain weight was decreased ($p \leq 0.01$) by 8% in the males. This finding was judged to correlate with the treatment-related decreases ($p \leq 0.05$) in several microscopic linear brain measurements: (i) thickness of the striatum on PND 21 (↓4-5% both sexes) and PND 70 (↓7% males only); (ii) thickness of the corpus callosum on PND 70 (↓16-21% both sexes); (iii) thickness of the hippocampal gyrus on PND 70 (↓7-9% both sexes); and (iv) height of the cerebellum on PND 70 (↓7% males only). It is noted that on PND 21, decrease in single morphometric parameter was seen in both sexes with the small magnitude (4-5%) whereas on PND 70, decrease in multiple morphometric measurements were seen in both sexes with greater magnitude (7-21%) than that seen in PND 21.

No treatment related effects were noted in the ≤50 mg/kg/day $F_1$ offspring.

**The offspring LOAEL was 200 mg/kg/day, based on decreases in body weight, body weight gains and several morphometric linear brain measurements in both sexes, and decreased absolute brain weight in the males on PND 70. The offspring NOAEL was 50 mg/kg/day.**

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6; OECD 426) in the rat.

## A.4.8 Metabolism

### 870.7485 Metabolism – Rat

In a metabolism study (MRID 41988401), single oral doses of $^{14}C$-tetrachlorvinphos (97%; Lot # 2587-180; $^{14}C$ in the phenyl group) were administered *via* gavage to three groups of Sprague-Dawley rats (5/sex) at (A) 5 mg/kg, (B) 5 mg/kg following 14 consecutive doses of unlabeled test material, or (C) 250 mg/kg, and urine (0-8 hours, 8-24 hours, and at 24-hour intervals up to 120 hours post dose) and feces (at 24-hour intervals up to 120 hours post dose) were collected. At 120 hours post dose, the rats were sacrificed, and whole blood/plasma, heart, lungs, liver, kidney, spleen, gastrointestinal tract, brain, ovaries/testes, total skin, and samples of muscle, fat, and bone, and the remaining carcass were collected for analysis.

Most of the radioactivity was recovered in urine (46%-60%) and feces (38%-56%) within 48 hours post dose. The greatest activity in the urine was found in the 0-8 hour interval for both sexes following the single and repeat 5 mg/kg dose, whereas the greatest activity following the 250 mg/kg dose was found in the 8-24 hour interval. Following the single 250 mg/kg dose, males excreted a similar % (≈50%) of the dose *via* the urine and feces, whereas the females excreted the majority *via* the urine (70% vs 30%). Following the single 5 mg/kg dose, males excreted 60%



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*via* the urine and 40% via the feces, and females excreted equal amounts (≈50%) *via* the urine and feces. Following the 14-day dosing period, both sexes excreted approximately equal amounts (≈50%) *via* the urine and feces. Only minor amounts (<0.5%) of the radiolabel were recovered from tissues after 5 days, with the GI tract, whole blood, and lungs showing the highest concentrations. The major metabolite in urine was trichloromandelic acid (18%-26%), and the major metabolite in feces was trichlorophenylethanol (>13%). Since the oral LD50 for female rats is lower than the male LD50, it is noteworthy that males of all groups excreted more total label as trichloromandelic acid, a more completely metabolized form of TCVP, whereas the high-dose females tended to excrete more of the label as desmethyl TCVP (with the phosphate group still attached to the remainder of the molecule), a compound that could be derived from TCVP with only a single metabolic step.

The metabolism study is classified as Acceptable/Guideline, and it satisfies the guideline requirement for a metabolism study (OPPTS 870.7485, OECD 417) in rodents.

#### 870.7600 Dermal Penetration Study – Rat

In a dermal absorption study (MRID 42111501), male CD rats (28/group/time point) were exposed dermally to doses of 0.01, 0.1, 1 or 5 mg/cm$^2$ radiolableled tetrachlorvinphos (97% a.i.), with some of each dose group sacrificed at 0.5, 1, 2, 4, or 10 hours. Additionally, there was a group of animals, sacrificed at 72 hours, in which the skin was washed at 10 hours. The area of the dermal application was washed to recover unabsorbed tetrachlorvinphos. Then, the skin, urine, feces, and carcass were analyzed for percent of total tetrachlorvinphos applied. For the group sacrificed at 10 hours, 84 % of the total tetrachlorvinphos applied (0.1 mg/cm$^2$) was recovered in the wash, and 9.57 % was in the skin, urine, feces, and carcass. The percent absorption increased with duration of exposure and generally decreased with increasing dose. The actual quantity of tetrachlorvinphos absorbed increased with increasing dose.

This study is classified as **Acceptable/Guideline**, and it satisfies the guideline requirement (OCSPP 870.7600) for a dermal penetration study in the rat.

### A.4.9 Immunotoxicity

#### 870.7800

In an immunotoxicity study (MRID # 48794701), Tetrachlorvinphos [100.05%, lot #100113] was administered to Crl:CD-1(ICR) female mice (10/dose) via oral gavage at dose levels of 0, 75, 300, or 1200 mg/kg/day for 28 consecutive days. An additional group of 10 positive control females received cyclophosphamide 10 mg/kg/day via gavage for 28 days. On Day 25 a single intravenous (IV) dose of 0.25 mL/animal of sheep red blood cells (SRBC) 2x10$^8$ cells/animal was administered to all animals. During the study, clinical signs, morbidity and mortality, bodyweight, food consumption, water consumption were measured and evaluated. On Day 29, blood samples were collected from the orbital sinus under isoflurance anaesthesia. Animals were euthanized

with carbon dioxide followed by exsanguination. All animals were subject to a complete necropsy examination. Spleen and thymus weights were recorded and immunotoxicity investigations by an Enzyme-linked immunosorbent assay (ELISA).

There were no treatment-related clinical signs and no unscheduled deaths. There were no treatment-related effects on body weights, food or water consumption. There were no treatment related necropsy findings. Absolute and relative mean thymus weight were statistically significantly lower ($p<0.05$) at 300 mg/kg/day group when compared with the vehicle control group. There were lower mean absolute thymus weight at 1200 mg/kg/day but it was not statistically significant; and there was no dose-dependent response in treated groups. Spleen weights in treated groups were not significantly different from the vehicle control group.

**For systemic toxicity, the NOAEL is 1200 mg/kg/day, the LOAEL was not established.**

When compare to the vehicle control group, the low and mid dose groups (75 and 300 mg/kg/day) had slightly higher anti-SRBC IgM levels, and the highest dose group (1200 mg/kg/day) had lower IgM levels. However, there were no statistically significant treatment-related effects on the specific anti-SRBC antibody response. High inter-individual variability was noted in all the treatment groups as well as in the control group. Evaluation of the individual animal data of this study did not show any trend or distribution that would demonstrate significant suppression of anti-SRBC IgM response. Animals in positive control group showed a statistically significant ($p< 0.05$) decrease of the anti-SRBC IgM response. This confirmed the ability of the test system to detect immuno-suppressive effects and confirmed the validity of the study design.

The NK cells activity assay was not performed. The toxicology database for tetrachlorvinphos does not reveal any evidence of treatment-related effects on the immune system. The overall weight of evidence suggests that this chemical does not directly target the immune system. Under HED guidance, a NK cells activity assay is not required at this time.

**For immunotoxicity, the NOAEL is 1200 mg/kg/day, tested above the limit dose; the LOAEL was not established.**

This immunotoxicity study is classified **acceptable/ guideline**, and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in mice.

## Special Studies

### Comparative Cholinesterase Studies

A series of studies (acute, repeat, gestational) was performed to investigate the effect of TCVP on brain and blood cholinesterase (ChE) activity and to determine the peak time of ChE

inhibition following both acute and repeated dosing in pre-weaning, young, maternal, and adult Sprague Dawley rats.

**Comparative Cholinesterase Assay - Repeat (11-days) Dose**:

In a comparative cholinesterase study (2012, MRID No.: 48773401), five groups of 10/sex of both 11 day old and young adult (~61 days) Crl:CD(SD) strain rats were dosed *via* gavage at dose levels of 0, 5, 10, 50 or 200 mg/kg/day of tetrachlorvinphos (TCVP) in methylcellulose. After 11 doses, the rats were sacrificed and assessed for red blood cell (RBC) and brain cholinesterase (ChE) activity.

*Systemic effects.* One female pup in the high dose group died after only two doses and its death was attributed to treatment. There was some decrease in body weight in this rat pup prior to death and the appearance was described as moderately dehydrated but no signs of typical ChE inhibition toxicity were reported. No other pups demonstrated clinical signs. There was an initial negative body weight gain in the adult males (days 1-2) but no clinical signs were evident in the adults.

**The LOAEL for systemic effects for both ages is 200 mg/kg/day, based on a single death of a female pup. The NOAEL is 50 mg/kg/day.**

*RBC ChE inhibition.* Adult males demonstrated a statistically significant reduction (13.3%) in RBC ChE level at 10 mg/kg/day. At 50 mg/kg/day, both male pups and adults had similar levels of inhibition (30% to 33%). At 200 mg/kg/day, the male pups were inhibited more (59.9%) than the male adults (36.3%). At 50 mg/kg/day, adult females demonstrated more inhibition (40.6%) than the female pups (19.2%) but at 200 mg/kg/day both female pups and adults had ~62% inhibition.

**The LOAEL for RBC ChE inhibition is 50 mg/kg/day for both sexes and both ages. The NOAEL is 10 mg/kg/day.**

*Brain ChE.* There was a dose-related decrease in brain ChE in adult females that was statistically significant at 10 mg/kg/day (↓12.2%), 50 mg/kg/day (↓42%), and 200 mg/kg/day (↓57.2%). Both sexes of pups displayed similar levels of brain ChE inhibition at 50 mg/kg/day (males ↓15.7%/females ↓18.7%) and 200 mg/kg/day (males ↓46.3%/females ↓45.1%), which were statistically significant. The adult males displayed statistically significant brain ChE inhibition at 50 mg/kg/day (↓14.9%) and 200 mg/kg/day (↓17.8%), although the magnitude of the response was similar at both dose levels.

**The LOAEL for brain ChE inhibition is 10 mg/kg/day, based on significant inhibition in adult females. The NOAEL is 5 mg/kg/day in adult females. The LOAEL for brain ChE inhibition is 50 mg/kg/day in male and female pups and in male adults. The NOAEL in male and female pups and in male adults is 10 mg/kg/day.**



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*Overall conclusion.* The main objective of this study was to determine if the pups are more sensitive than the adults to the cholinesterase inhibitory potential of TCVP. A comparison of the magnitude of cholinesterase inhibition in the brain and RBC compartments in the females shows the female pups with less inhibition (at 50 mg/kg/day) or a comparable amount of inhibition (at 200 mg/kg/day) as the female adults. For the males, a similar magnitude of inhibition was displayed in the pups and adults at 50 mg/kg/day, although the male pups displayed a greater % inhibition in both compartments at 200 mg/kg/day than the adult males. Based on assignment of the NOAEL and LOAEL, there was no demonstration for increased sensitivity of the pups relative to the adults for either RBC or brain ChE. Although the magnitude of brain inhibition in the male pups was greater than in the male adults, this occurred only at the 200 mg/kg/day dose level. The benchmark dose analysis of the brain cholinesterase data does not show the male pups to be more sensitive.

A benchmark dose analysis of the repeat dose cholinesterase data (RBC and brain) was performed that provides both the $BMD_{10}$ and $BMDL_{10}$ of adults and PND11 pups.

| **$BMD_{10}$s and $BMDL_{10}$s for Adult Rat and PND 11 Pup Cholinesterase** | | | | |
|---|---|---|---|---|
| | **RBC $BMD_{10}$** | **RBC $BMDL_{10}$** | **Brain $BMD_{10}$** | **Brain $BMDL_{10}$** |
| Adult males | 7.7178 | 3.5942 | 33.803 | 24.4489 |
| Adult females | 8.6762 | 6.1335 | 7.1764 | 5.4980 |
| PND 11 males | 20.4688 | 15.9719 | 33.4825 | 26.5707 |
| PND 11 females | 20.5608 | 13.1692 | 24.2224 | 18.9412 |

***Classification:*** The classification of this repeat dose *in vivo* comparative cholinesterase inhibition study is Acceptable/Non-Guideline. It does not satisfy a guideline requirement. It satisfies the generic data call-in requirement for TCVP for a comparative cholinesterase study in adult rats versus postnatal day (PND) 11 rat pups.

**Comparative Cholinesterase Assay - Acute Dose**

In an acute comparative cholinesterase study (MRID 48773401a), TCVP (98.99% a.i.; Batch # TX100405)] was administered to 10 Crl:CD (SD) adult rats/sex/dose, 10 Crl:CD (SD) postnatal day (PND) 11 pups/sex/dose, and 10 Crl:CD(SD) PND 21 pups/sex/dose once *via* gavage (10 mL/kg) at dose levels of 0 (1% w/v aqueous methylcellulose), 10, 50, 150, or 300 mg/kg. Viability, clinical signs, body weights, and brain weights were evaluated. Approximately three hours post dose, red blood cell (RBC) and brain acetylcholinesterase (AChE) levels were determined.

There were no treatment-related deaths. Treatment-related clinical signs included soft or liquid feces in several adult males at 150 mg/kg and 300 mg/kg, decreased motor activity in PND 21 males and females at 150 mg/kg and 300 mg/kg, and urine-stained abdominal fur in PND 21 rats at 300 mg/kg. There were no clinical signs in the PND 11 pups or adult females.

Cholinesterase inhibition was displayed in both compartments in all age groups at all dose levels, with one exception. The magnitude of the response in the adult female rats (RBC and brain) was lower than in the adult male rats and in both sexes of PND 11 and PND 21 pups.

For both compartments, the magnitude of the response was comparable among the age groups and similar between the sexes, with the exception of the adult female rats. *All groups showed a similar response in both the RBC and brain cholinesterase compartments at each dose level.*

**The NOAEL for adult rats (both sexes) for RBC and brain cholinesterase inhibition following an acute oral dose was not determined. The LOAEL for adult rats is 10 mg/kg.**

**The NOAEL for PND 21 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 21 pups is 10 mg/kg.**

**The NOAEL for PND 11 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg.**

This comparative study of RBC and brain cholinesterase activities following acute oral treatment with TCVP in adult and neonatal (PND 11 and PND 21) rats is classified **Acceptable/Non-guideline.** It does not satisfy any guideline requirement; however, it does satisfy the data requirement for TCVP for an acute comparative cholinesterase activity between adult and young rats.

**COMMENT**: This acute exposure comparative cholinesterase study final report was embedded within the repeat dose comparative cholinesterase study report (MRID 48773401); it should have been submitted as a separate study report and been given a unique MRID #. The results of the Benchmark dose analysis for the acute study are provided below.

| TCVP/Study | Sex/Age | Compartment | BMD Results (mg/kg) | |
|---|---|---|---|---|
| | | | $BMD_{10}$ | $BMDL_{10}$ |
| MRID 48773401a Acute CCA | Male PND11 | Brain | 5.1 | 4.5 |
| | Female PND11 | Brain | 5.9 | 4.8 |
| MRID 48773401a Acute CCA | Male PND11 | RBC | 5.0 | 4.1 |
| | Female PND11 | RBC | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | Male PND21 | Brain | 3.5 | 3.2 |
| | Female PND21 | Brain | 5.3 | 3.7 |
| MRID 48773401a Acute CCA | Male PND21 | RBC | 3.2 | 2.8 |
| | Female PND21 | RBC | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Male Adult | Brain | 7.4 | 5.6 |
| | Female Adult | Brain | 11.6 | 9.8 |
| MRID 48773401a | Male Adult | RBC | 6.5 | 3.6 |

| | | | | |
|---|---|---|---|---|
| Acute CCA | Female Adult | RBC | 14.9 | 11.2 |

**Comparative Cholinesterase Assay - Gestational Exposure**

In a maternal and fetal exposure study (2010, MRID 48291101), tetrachlorvinphos (TCVP) (purity 99.6%, Lot No. NJ250RB08) dissolved in 1% aqueous (w/v) methylcellulose was administered to pregnant female Crl:CD(SD)IGS BR VAF/Plus rats via gavage once daily on days 6 through 21 of gestation at doses of 0, 75, 150 or 300 mg/kg/day. On gestation day 21 (GD 21), within 2 hr of the last dose, whole blood samples and brains were collected from the dams for cholinesterase (ChE) assessment. Dams were Caesarean-sectioned and pooled fetal blood samples and brains were collected for ChE assessment.

***Maternal Systemic and Litter Effects:*** All dams survived until scheduled sacrifice and no adverse clinical observations were reported. No Caesarean-sectioning or litter parameters were affected. Body weight *gains* and food consumption in dams were reduced in the 150 and 300 mg/kg/day groups. No gross lesions were observed during necropsy of the dams. There were no fetal gross external alterations and fetal body weights, brain absolute and relative weights were comparable among the dose groups. Since the main purpose of this study was to assess differential sensitivity between the dams and the fetuses, no assignment of a NOAEL and LOAEL for maternal systemic and litter effects is being made.

***RBC ChE***: Neither the dams nor the fetuses demonstrated RBC ChE inhibition. In dams the values were 5.1%, 15% and 3% lower than the control for the low, mid and high doses, respectively. Interpretation of the fetal RBC data was confounded because only 1 or two samples were available and no sample was available for the mid dose group. *The RBC ChE data are considered unacceptable because the repeat dosing study (2012, 48773401) conducted in the same laboratory in the same strain of rat was clearly able to demonstrate RBC ChE inhibition at 50 and 200 mg/kg/day in females. There was no way to compare adult and fetal RBC ChE.*

***Plasma ChE***. Plasma ChE inhibition in dams was dose dependent being 62%, 71% and 77% for the low, mid and high dose groups, respectively. Fetal plasma ChE values were 22%, 18.5% and 20.8% less than the control for the low, mid and high dose groups, respectively. The lack of a dose response raises the question as to whether these lower values are actually inhibition. However, there is no indication that the fetuses are more sensitive than the dams for this compartment.

***Brain ChE.*** Brain ChE inhibition was also dose dependent in dams; *i.e.*, 31%, 44% and 67% for the low, mid and high doses, respectively. Fetal brain ChE values were 10%, 20.9% and 20.8% lower than the controls for the low, mid and high dose groups, respectively. Similar to the plasma ChE data, there is no dose response to support a conclusion that these lower values are actually inhibition. However, there is no indication that the fetal brain ChE is more sensitive to inhibition by TCVP than the dams.

This *in vivo* comparative ChE study is classified as **Acceptable/non-guideline**. The study does not satisfy a guideline requirement. It satisfies a data call-in-requirement for TCVP for a gestational comparative ChE study in maternal rats versus fetal rats, although it is to be noted that the dose levels selected are way too high. However, from the data available, no increase in sensitivity was evident. RBC ChE inhibition was not demonstrated in the dams or fetuses (no data), and the flat dose response curves for the brain ChE in both pups and adults confound the interpretation of the study. However, no additional gestational CCA study is being requested at this time because there is no indication that the fetuses were more affected than the dams.

**Comparative Cholinesterase Assay - Acute Exposure**

In an acute relative cholinesterase (ChE) sensitivity study (2010, MRID 48294601), tetrachlorvinphos (TCVP) (purity 99.6%, Lot No. NJ250RB08) was administered at doses of 0, 75, 150 or 300 mg/kg body weight dissolved in 1% aqueous (w/v) methylcellulose to Crl:CD(SD)IGS BR VAF/Plus strain young adult (about 42 days old) and to postnatal day (PND) 11 and 21 neonatal rats via a single oral (gavage) dose. Four rats/sex/dose were sacrificed on pretest and at 1, 2, 3, 4, 8 and 24 hours after dosing.

***Systemic effects.*** All pups and all adult rats groups survived. There were no adverse clinical or necropsy observations related to the TCVP administration, and no effects on body or brain weights were reported. Since this is a short term study primarily designed to assess for comparative sensitivity to ChE inhibition, no NOAEL or LOAEL for systemic effects will be assigned.

***General comments on ChE assessment.*** Only four rats/sex were available for assessment at each of the seven assessment times. Many of the RBC and plasma ChE assessments were made on only 0 (no sample available), 1, 2, or 3 samples because of loss of sample. In addition, duplicate samples that did not replicate contributed to the low number of sample to provide a meaningful mean. Brain ChE also appeared to be affected by the low number of samples. The results for all three enzyme sources indicated that there was inhibition at all doses but there was poor dose response with the degree of apparent inhibition at the higher doses often less that at the low dose of 75 mg/kg/day. There was also a lack of temporal concordance with high apparent inhibition at one time, a much lower degree at the following time and back to the higher level at the next time point. Another problem is that there was more or similar apparent inhibition at the low dose of 75mg/kg in this acute study than there was in the repeat dosing studies (2012, MRID 48773401, eleven daily doses) at 200 mg/kg/day and in the gestational study (2010, MRID 48291101, fifteen daily doses) at 150 mg/kg/day. Also, the repeat dosing study clearly indicated that there was no increase in sensitivity of the pups relative to the adults with regard to potential inhibition by TCVP. In this acute study, there were several comparisons among the PND11, PND21 and adults that suggested the pups were more sensitive.

Overall, there is little confidence in the data mainly because of the lack of clear dose and temporal responses.

***Benchmark Dose (BMD) modeling.*** BMD modeling was performed but could not be done with the RBC data or for the PND11 brain data because of too few samples and/or the data would not otherwise fit the models. BMD modeling for the brain data (for the three hour assessment time) indicated that for males, the adults may be slightly more sensitive than the PND 21 pups but the females were considered similar with respect to the $BMD_{10}$ and $BMDL_{10}$.

| **TCVP/Study** | **Sex/Age** | **Compartment** | **BMD Results** (mg/kg/day) | |
|---|---|---|---|---|
| | | | **$BMD_{10}$** | **$BMDL_{10}$** |
| MRID 48294601 Acute CCA | Adult male | Brain | 6.76716 | 5.02249 |
| MRID 48294601 Acute CCA | Adult female | Brain | 11.2932 | 4.55107 |
| MRID 48294601 Acute CCA | Male pup PND 21 | RBC | 16.8647 | 9.71265 |
| MRID 48294601 Acute CCA | Female pup PND 21 | Brain | 9.80073 | 4.6942 |
| MRID 48294601 Acute CCA | Male pup PND 21 | Brain | 11.246 | 6.76389 |

This study is classified as A**cceptable/Non-Guideline.** The study does not satisfy a guideline requirement. It satisfies a data call-in-requirement for TCVP for an acute comparative ChE study in adult, PND 21, and PND 11 pups, although there is too much variability in the data to make meaningful comparisons for sensitivity for RBC. Brain ChE data also had problems with variability and dose response to compare for sensitivity. However, from the data available, there is no conclusive evidence of increased sensitivity. No additional acute CCA study is being requested at this time because there is no indication that the young animal was more affected than the adult. NOTE: An additional acute comparative cholinesterase study (MRID 48773401a) was located and is discussed above.

## Appendix B. Results for BMD/BMDL modeling for TCVP

### B.1. Summary of OPP's ChE Policy & Use of BMD Modeling

OPP's AChE policy (USEPA, 2000[1]) describes the manner in which AChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or cholinesterase (ChE) inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung etc) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and RBC) ChE. Blood measures do not represent the target tissue, per se, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.



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Refinements to OPP's use of AChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often the decreasing exponential empirical model has been used.

OPP does not have a defined BMR for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the $BMD_{10}$ is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the $BMD_{10}$.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity in the brain compartment and is a response level close to the background brain AChE level. With respect to biological considerations, a change in 10% brain AChE inhibition is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC AChE inhibition, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC AChE inhibition but BMRs up to 20% could be considered on a case by case basis as long as such PODs are protective for brain AChE inhibition, potential peripheral inhibition, and clinical signs of neurotoxicity.

## B.2. Summary Tables of Benchmark Dose (BMD) Analyses

BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using an exponential model for continuous data (Bever and Holman, D435480, 9/1/2016). The data selected for evaluation consisted of decreased brain and red blood cell (RBC) cholinesterase (AChE) activities from rats in an acute comparative cholinesterase assay (CCA; MRID 48773401a). The results of the acute dosing BMD analyses are summarized below in Table B.1.

**Table B.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on TCVP, Acute Oral Dosing Study in Rats.**

| Study | Age Sex | Brain $BMD_{10}$ | Brain $BMDL_{10}$ | RBC $BMD_{10}$ | RBC $BMDL_{10}$ |
|---|---|---|---|---|---|
| MRID 48773401a Acute CCA | PND 11 Male | 5.1 | 4.5 | 5.0 | 4.1 |
| MRID 48773401a Acute CCA | PND 11 Female | 5.9 | 4.8 | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | PND 21 Male | 3.5 | 3.2 | 3.2 | 2.8 |

| | | | | | |
|---|---|---|---|---|---|
| MRID 48773401a Acute CCA | PND 21 Female | 5.3 [a] | 3.7 | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Adult Male | 7.4 | 5.6 | 6.5 | 3.6 |
| MRID 48773401a Acute CCA | Adult Female | 11.6 [a] | 9.8 | 14.9 | 11.2 |

CCA = Comparative Cholinesterase Assay

[a]Although the model chosen resulted in program warning that "the model may not adequately describe the data", fit was considered adequate based on similarity to values from other data sets, plausibility after considering empirical data (ground-truthing), and visual assessment of the fit.

Previously, Benchmark Dose (BMD) analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using an exponential model for continuous data [2]. The Hill model was also performed for some data sets, but did not result in the best fit for the data. The data selected for evaluation consisted of decreased brain and red blood cell (RBC) cholinesterase (ChE) activities. Data were analyzed from a 21-day oral toxicity study (MRID 45570601), a 13-week subchronic oral toxicity study (MRID 43371201), a 2 year chronic oral toxicity study (MRID 42980901); a gestational comparative cholinesterase assay (MRID 48291101); and a 28-day inhalation toxicity study (MRID 48803501). The results of the repeated oral and inhalation dosing BMD analyses are summarized below in Table B.2. Good model fit ($p>0.1$) was obtained for the majority of the analyses, with any exceptions being noted.



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| Table B.2. Results of BMD Exponential Modeling for Brain and RBC ChE Data on TCVP, Repeated Oral Dosing Studies in Rats, Ranging in Duration from 21 days to 2 years. | | | | |
|---|---|---|---|---|
| **TCVP Study** | **Age/Sex** | **Compartment** | **BMD Results** | |
| | | | **$BMD_{10}$** | **$BMDL_{10}$** |
| MRID 43371201 13W Oral – 13 Weeks | Adult Male | Brain | No dose response (analysis not performed) | |
| | Adult Female | Brain | No dose response | |
| | Adult Male | RBC | 61.6 mg/kg/day | 26.3 mg/kg/day |
| | Adult Female | RBC | 10.5 mg/kg/day | 8.0 mg/kg/day |
| MRID 42980901 Chronic Oral Tox – 364, 539, and 721 Days | Adult Female | RBC | No dose-response effect was observed at 364, 539, or 721 days | |
| MRID 45570601 21D Oral Tox – 21 Days | Adult Female | Brain | 14.7 mg/kg/day | 12.2 mg/kg/day |
| | | RBC | 9.9 mg/kg/day | 6.7 mg/kg/day |
| MRID 48803501 28D Inhalation – 28 Days | Adult Male | RBC | 0.122 mg/L | 0.022 mg/L |
| | Adult Female | RBC | 0.394 mg/L | 0.050 mg/L |

[1] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.
[2] J. Bever. Tetrachlorvinphos: Benchmark Dose Analysis of Subchronic and Chronic Studies to Support Derivation of Points of Departure. 5/20/2014. TXR # 0056970. D420286.

## Appendix C. Methodologies for HEC Calculations

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (e.g., systemic vs. portal-of-entry) and the pharmacokinetic (PK) **but not pharmacodynamic** (PD) differences between animals and humans. Based on the EPA's RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (e.g., systemic vs. portal-of-entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (e.g., acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid. These assumptions, in turn, vary depending on the type of toxicity observed. Thus the derivation of a HEC for inhaled gases is described by the following equation:

$$HEC = POD_{study} * \frac{D_{\text{animal exposure (hrs / day)}}}{D_{\text{human exposure (hrs / day)}}} * \frac{W_{\text{animal exposure (days / wk)}}}{W_{\text{human exposure (days / wk)}}} * RGDR$$

Where:
$POD_{study}$: Point of departure identified in the critical toxicology study
$D_{\text{animal exposure}}$: Duration of animal exposure (hrs/day; days/wk)
$D_{\text{anticipated exposure}}$: Anticipated human duration of exposure (hrs/day; days/wk)
RGDR: Regional Gas Dose Ratio

Calculations used to estimate the inhalation risk to humans from aerosols are dependent not on the RGDR as for gases, but on the regional deposited dose ratio (RDDR). Inhalation studies using aerosols characterize particulate exposure by defining the particulate diameter (mass median aerodynamic diameter [MMAD]) and the geometric standard deviation ($\sigma_g$), which is then used to determine the RDDR. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the rth region or target tissue.

$$RDDR_r = \frac{(RDD_r/\text{Normalizing Factor})_A}{(RDD_r/\text{Normalizing Factor})_H}$$

As with calculations for gases, the r regions and potential target tissues are the three respiratory regions (ET, TB, PU). The RDDR is easily calculated by using a software program designed specifically for computing the RDDR from the MMAD and $\sigma_g$ defined from an aerosol inhalation study. The values for the species-specific parameters used to calculate the RDDR are



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provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry."

**Regional Deposited Dose Ratio (RDDR) for TCVP**

MMAD = 2.57
Sigma g = 3.79

| SPECIES | Body Weight (g) | Minute Ventilation (VE, ml) |
|---|---|---|
| rat | 267 | 189.8 |
| human | 70000 | 13800.0 |

| | Extrarespiratory BW (g) | deposited fraction |
|---|---|---|
| rat | 267 | 0.460 |
| human | 70000 | 0.657 |
| RATIO | 0.004 | 0.700 |

RDDR = $(VE/BW)_{animal}/(VE/BW)_{human}$ * deposited $fraction_{animal}$/deposited $fraction_{human}$
= $(189.8/267)_{animal}/(13800/70000)_{human}$ * 0.460/0.657
= 2.525

The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the PK differences **but not the PD differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

***C.1. HEC Calculations for Residential Exposure:***

*Assume residents will be exposed for 24 hrs/day and 7 days/week:*

*HEC = $NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR*

*Residential Bystander HEC = 0.022 mg/L * (6/24) * (5/7) * 2.525 = 0.0099 mg/L*
*Residential Handler Outdoor HEC = 0.022 mg/L * 2.525 = 0.0555 mg/L*



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| Table C.1.1. HEC Array for Residential Handler Risk Assessment. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 8 | 5 | 5 | 2.525 | 0.0555 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Table C.1.2. HEC Array for Residential Bystander Risk Assessment. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 24 | 5 | 7 | 2.525 | 0.099 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Key for Array Tables | |
|---|---|
| *LOAEL*: Lowest-observed adverse-effect level | *RRDR*: Regional Deposited Dose Ratio |
| *NOAEL*: No-observed adverse-effect level | *HEC*: Human-Equivalent Concentration |
| *Da*: Daily animal exposure (hrs/day) | *inter*: Interspecies extrapolation UF |
| *Dh*: Anticipated daily human exposure (hrs/day) | *intra*: Intraspecies variation UF |
| *Wa*: Weekly animal exposure (days/week) | *UF*: Other UF(s) |
| *Wh*: Anticipated weekly human exposure (days/week) | *ER:* Extra-respiratory effects |

***Route-to-Route Extrapolation***

*More information and details in: Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/98.*

*HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes. An activity factor is used to account for increased exposure resulting from increased respiration.*

*Using the HEC calculated (based on an increase in RBC cholinesterase inhibition in both sexes), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:*

*HED (mg/kg/day) = Dose (systemic HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg*

*Where:*

*A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route.*

*CF = conversion factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of J. Whalen and H. Pettigrew, 10/10/98).*

*D = duration; duration of daily animal or human exposure (hours).*

*AF = activity factor; animal default is 1. For humans the value varies with ventilation*

**11.8 L/hr/kg is the typical breathing rate assumed for humans.*

*Therefore, the residential HED for TCVP is calculated as follows:*

***Residential Handler HED:*** *(0.056 mg/L) x 11.8 L/hr/kg x 2 hr x 1 = 1.31 mg/kg/day*

***C.2. HEC Calculations Occupational Exposure:***

*Assume workers will be exposed for 8 hrs/day and 5 days/week:*

*HEC = $NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR*

Occupational - HEC = 0.022mg/L * (6/8) * (5/5) * 2.525 = 0.0416 mg/L.

**Table C.1.3. HEC Array for Occupational Risk Assessment.**

| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 8 | 5 | 5 | 2.525 | 0.0416 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Key for Array Tables | |
|---|---|
| *LOAEL*: Lowest-observed adverse-effect level | *RRDR*: Regional Deposited Dose Ratio |
| *NOAEL*: No-observed adverse-effect level | *HEC*: Human-Equivalent Concentration |
| *Da*: Daily animal exposure (hrs/day) | *inter*: Interspecies extrapolation UF |
| *Dh*: Anticipated daily human exposure (hrs/day) | *intra*: Intraspecies variation UF |
| *Wa*: Weekly animal exposure (days/week) | *UF*: Other UF(s) |
| *Wh*: Anticipated weekly human exposure (days/week) | *ER:* Extra-respiratory effects |



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**Route-to-Route Extrapolation**

More information and details in: Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/98.

HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral-equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes. An activity factor is used to account for increased exposure resulting from increased respiration.

Using the HEC calculated (based on an increase in RBC cholinesterase inhibition in both sexes), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:

HED (mg/kg/day) = Dose (systemic HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg

Where:

| | | |
|---|---|---|
| A | = | absorption; ratio of deposition and absorption in respiratory tract compared to absorption by the oral route. |
| CF | = | conversion factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of J. Whalen and H. Pettigrew, 10/10/98). |
| D | = | duration; duration of daily animal or human exposure (hours). |
| AF | = | activity factor; animal default is 1. For humans, the value varies with ventilation rates |

Therefore, the occupational HED for TCVP is calculated as follows:

**Occupational Handler HED:** 0.042 mg/L x 11.8 L/hr/kg x 1.0 x 8 hr = 3.94 mg/kg/day

Based on the current TCVP label, HED believes exposures can be short- (1-30) or intermediate- (1 to 6 months) term in duration. Long-term exposures are not anticipated for TCVP based on proposed labeled uses. For the short- and intermediate-term scenarios, inhalation data from the 28-day inhalation rodent study was most appropriate for determining HECs. In the RfC methodology, different HECs may be calculated for the same experimental NOAEL due to the following:

1. Different algorithms are used to derive HECs for systemic versus portal-of-entry effects. Typically, HECs are calculated separately for systemic versus portal-of-entry effect. For TCVP, extra-respiratory effects were observed and, therefore, only extra-respiratory HECs were derived.

Time adjustments are traditionally needed for non-occupational (bystander) versus occupational exposure scenarios. Traditionally, HECs for non-occupational exposure are based on the number of hours an individual may be at home. Therefore, the most conservative estimate of hours spent at home would be 24 hours/day and 7 days/week. In comparison, the average workweek for an occupational worker is 8 hours/day and 5 days/week. The HEC array table reflects the time adjustment in the calculations.



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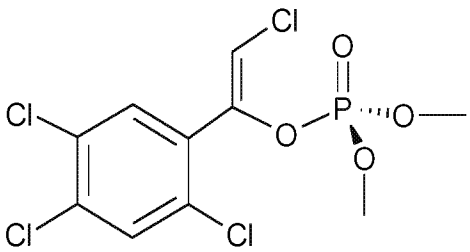
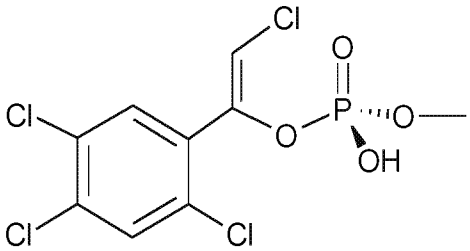
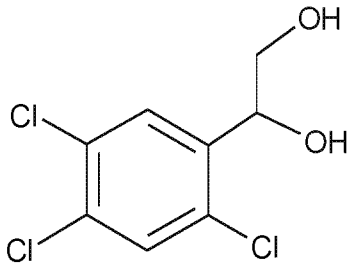
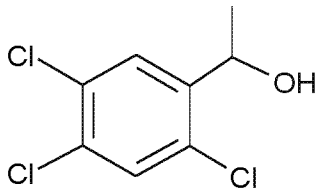
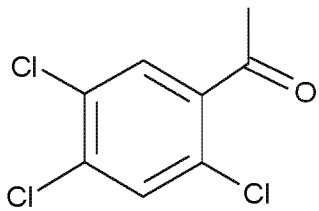
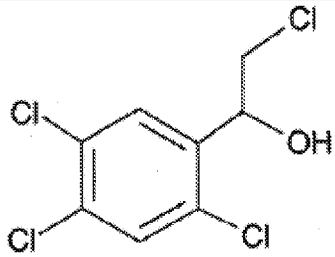
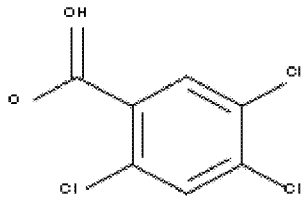
## Appendix D. Physical/Chemical Properties for Tetrachlorvinphos

| Table D.1 Physicochemical Properties of the Technical Grade Test Compound: Tetrachlorvinphos | | |
|---|---|---|
| Parameter | Value | Reference [1] |
| Melting point/range | 94.5 °C | (MRID 41222503) |
| pH | 5.5; 1% solution | (MRID 41222503) |
| Density | 0.83 g/mL | (MRID 41222503) |
| Water solubility | (25°C) 11.6 g/L | (MRID 41222503) |
| Solvent solubility | (mg/100mg at 25°C)<br>chloroform 80<br>methanol 21<br>acetone 44<br>hexane 0.8<br>toluene 28 | (MRID 41222503) |
| Vapor pressure | (25°C) 2.6 x $10^{-7}$ mm Hg | (MRID 41222503) |
| Dissociation constant, $pK_a$ | non-ionizable | (MRID 41222503) |
| Octanol/water partition coefficient, Log($K_{OW}$) | 3350 average $K_{OW}$ at 25 °C | (MRID 41222503) |
| UV/visible absorption spectrum | Not available | |

[1] Cited reference was reviewed under CB No. 7468, 4/3/91, R. Perfetti.

## Appendix E. TCVP and Metabolites

| Chemical Name | Structure | Physical/Chemical Properties[1] |
|---|---|---|
| **Tetrachlorvinphos**<br><br>IUPAC: (*Z*)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate<br><br>CAS: (*1Z*)-2-chloro-1-(2,4,5-trichlorophenyl)ethenyl dimethyl phosphate<br><br>CAS Reg. No. 22248-79-9<br><br>COP(=O)(OC)OC(=CCl)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 365.96 g/mol<br>VP: 2.6E-07 torr<br>Solubility: 11.6 mg/L<br>Log Kow: 3.53<br>Koc: 520-1100 L/$kg_{oc}$ |
| **Des-O-methyl tetrachlorvinphos**<br><br>IUPAC: (*Z*)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl methyl phosphate<br><br>CAS: (*1Z*)-2-chloro-1-(2,4,5-trichlorophenyl)ethenyl methyl phosphate<br><br>COP(=O)(O)OC(=CCl)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 351.94 g/mol<br>VP: 4.27E-08 torr<br>Solubility: 3.768 mg/L<br>Log Kow: 3.75<br>Koc: 702-827 L/$kg_{oc}$ |
| **1-(2,4,5-trichlorophenyl)ethanediol**<br><br>C(O)(CO)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 241.5 g/mol<br>VP: 4.37E-06 torr<br>Solubility: 250 mg/L<br>Log Kow: 2.37<br>Koc: 29-36 L/$kg_{oc}$ |
| **TCPEol (SD 15509, AA849)**<br><br>1-(2,4,5-trichlorophenyl)ethanol<br>1-(2,4,5-trichlorophenyl)ethan-1-ol<br><br>CC(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 225.5 g/mol<br>VP: 2.37E-04 torr<br>Solubility: 123 mg/L<br>Log Kow: 3.43<br>Koc: 319-359 L/$kg_{oc}$ |
| **TCPEone (CO300)**<br><br>2,4,5-trichloroacetophenone<br><br>CC(=O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 223.5 g/mol<br>VP: 6.32E-03 torr<br>Solubility: 27.4 mg/L<br>Log Kow: 3.61<br>Koc: 492-1,828 L/$kg_{oc}$ |

| Chemical Name | Structure | Physical/Chemical Properties[1] |
|---|---|---|
| **TCCEol (SD15125, AA576)**<br><br>l-(2,4,5-trichlorophenyl)-2-chloroethanol<br><br>C(Cl)C(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 260 g/mol<br>VP: 2.11E-05 torr<br>Solubility: 250 mg/L<br>Log Kow: 3.68<br>Koc: 494-608 L/$kg_{oc}$ |
| **TCBA (SD 15917)**<br><br>2,4,5-Trichlorobenzoic acid<br><br>C(=O)(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 225.5 g/mol<br>VP: 5.52E-04 torr<br>Solubility: 35.3 mg/L<br>Log Kow: 3.47<br>Koc: 157-166 L/$kg_{oc}$ |

1. Physical and chemical properties for degradates obtained through EPISuite 4.11.

## Appendix F. International MRLs and U.S. Tolerances

| Table F.1. Tetrachlorvinphos: Summary of U.S. and International Tolerances and Maximum Residue Limits. | | | | |
|---|---|---|---|---|
| Commodity | U.S. Tolerances, 40 CFR §180.252 [1] | | Codex MRL | Canada's MRL [2] |
| | Established U.S. Tolerance, ppm | Reassessed U.S. Tolerance, ppm | | |
| Milk, fat (reflecting negligible residues in whole milk) | 0.5 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | milk: 0.1 (of which not more than 0.04 ppm is tetrachlorvinphos *per se*) | None | None |
| Cattle and Hog, Fat | Fat of cattle and hog: 0.2 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | Fat of cattle and hog: 1.0 (of which not more than 0.8 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Muscle | meat of cattle and hog: 2.0 (of which not more than 2.0 ppm is tetrachlorvinphos *per se*) | meat of cattle and hog: 0.3 (of which not more than 0.2 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Kidney | kidney of cattle and hog: 1.0 (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | meat byproducts of cattle and hog : 1.0 (of which no more than 0.6 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Liver | liver of cattle and hog: 0.5 (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | | None | 1.5 [3] |

| Table F.1. Tetrachlorvinphos: Summary of U.S. and International Tolerances and Maximum Residue Limits. | | | | |
|---|---|---|---|---|
| Commodity | U.S. Tolerances, 40 CFR §180.252 [1] | | Codex MRL | Canada's MRL [2] |
| | Established U.S. Tolerance, ppm | Reassessed U.S. Tolerance, ppm | | |
| Cattle and Hog, Meat byproducts | meat byproducts, except kidney and liver of cattle and hog: 1.0 | | None | 1.5 [3] |
| Eggs | 0.2 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.3 (of which not more than 0.03 ppm is tetrachlorvinphos *per se*) | None | None |
| Poultry, muscle | meat of poultry: 3.0 (of which not more than 3.0 ppm is tetrachlorvinphos *per se*) | meat of poultry: 0.4 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, liver | 2.0 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | meat byproducts of poultry: 20 (of which not more than 6.0 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, meat byproducts | meat byproducts, except liver, of poultry: 2.0 | meat byproducts of poultry: 20 (of which not more than 6.0 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, fat | 7.0 (of which not more than 7.0 ppm is tetrachlorvinphos *per se*) | 1.4 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Apples | None | None | None | 10 |
| Grapes | None | None | None | 10 |

## Appendix G. Summary of Residential Handler Non-Cancer Exposures and Risks

| Table G.1. Residential Handler Non-cancer Dermal and Inhalation Dose Assuming a Liquid or Dust Formulation for Pet Collars. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal Dose (mg/kg/day)[3] | Inhalation Dose (mg/kg/day)[4] |
| Assume Liquid Formulation -- Use of Spot-On Exposure Data (based on 2012 Residential SOPs) | | | | | | | |
| Application of TCVP Collars | 2596-49: Cat | 120 | Negligible | 0.0036: 11 gram collar | 2 animals treated per day | 0.0012 | Negligible |
| | 2596-50, 62: Dog | | | 0.0061: 19 gram collar | | 0.0020 | |
| | | | | 0.010: 32 gram collar | | 0.0034 | |
| | 2596-63: Cat | | | 0.0048: 15 gram collar | | 0.0016 | |
| | | | | 0.0055: 17 gram collar | | 0.0018 | |
| | 2596-83: Cat | | | 0.0039: 12 gram collar | | 0.0013 | |
| | | | | 0.0080: 25 gram collar | | 0.0027 | |
| | 2596-84: Dog | | | 0.0061: 19 gram collar | | 0.0021 | |
| | | | | 0.010: 32 gram collar | | 0.0034 | |
| | 2596-139: Cat | | | 0.0032: 10 gram collar | | 0.0011 | |
| | 2596-139: Dog | | | 0.016: 50 gram collar | | 0.0054 | |
| | 11556-164: Dog | | | 0.0072: 24 gram collar | | 0.0024 | |
| | 11556-165: | | | 0.0045: | | 0.0015 | |

| Table G.1. Residential Handler Non-cancer Dermal and Inhalation Dose Assuming a Liquid or Dust Formulation for Pet Collars. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal Dose (mg/kg/day)[3] | Inhalation Dose (mg/kg/day)[4] |
| | Cat | | | 15 gram collar | | | |
| **Assume Dust Formulation -- Use of TCVP Dust Applicator Exposure Data (MRID 45519601)** | | | | | | | |
| Application of TCVP Collars | 2596-49: Cat | 1,700 | 3.1 | 0.0036: 11 gram collar | 2 animals treated per day | 0.017 | 0.00033 |
| | 2596-50, 62: Dog | | | 0.0061: 19 gram collar | | 0.029 | 0.00055 |
| | | | | 0.010: 32 gram collar | | 0.049 | 0.00092 |
| | 2596-63: Cat | | | 0.0048: 15 gram collar | | 0.023 | 0.00043 |
| | | | | 0.0055: 17 gram collar | | 0.026 | 0.00049 |
| | 2596-83: Cat | | | 0.0039: 12 gram collar | | 0.018 | 0.00035 |
| | | | | 0.0080: 25 gram collar | | 0.038 | 0.00072 |
| | 2596-84: Dog | | | 0.0061: 19 gram collar | | 0.029 | 0.00055 |
| | | | | 0.010: 32 gram collar | | 0.049 | 0.00092 |
| | 2596-139: Cat | | | 0.0032: 10 gram collar | | 0.015 | 0.00029 |
| | 2596-139: Dog | | | 0.016: 50 gram collar | | 0.076 | 0.00144 |
| | 11556-164: Dog | | | 0.0072: 24 gram collar | | 0.034 | 0.00065 |
| | 11556-165: Cat | | | 0.0045: 15 gram collar | | 0.021 | 0.00041 |

| Table G.2. Residential Handler Non-cancer Risk Estimates Assuming 1/99 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Reg. No.** | **Maximum Application Rate[1] (lb ai/pet)** | **Amount Handled Daily[2]** | **Combined 1/99 Liquid/Dust Dermal Dose (mg/kg/day)[3]** | **Combined 1/99 Liquid/Dust Inhalation Dose (mg/kg/day)[4]** | **Combined 1/99 Liquid/Dust Ratio Inhalation MOE[5]** |
| | | | | | | **LOC = 300** |
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0170 | 0.00032 | 4,100 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0285 | 0.00054 | 2,400 |
| | | 0.010: 32 gram collar | | 0.0481 | 0.00092 | 1,400 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0225 | 0.00043 | 3,100 |
| | | 0.0055: 17 gram collar | | 0.0255 | 0.00049 | 2,700 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0180 | 0.00034 | 3,800 |
| | | 0.0080: 25 gram collar | | 0.0376 | 0.00072 | 1,800 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0285 | 0.00054 | 2,400 |
| | | 0.010: 32 gram collar | | 0.0481 | 0.00092 | 1,400 |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0150 | 0.00029 | 4,600 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0751 | 0.00143 | 920 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0338 | 0.00064 | 2,000 |
| | 11556-165: Cat | 0.0045: 15 gram collar | | 0.0211 | 0.00040 | 3,300 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 1/99 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.01) + (Dust dermal dose * 0.99)

4 Combined 1/99 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.01) + (Dust dermal dose * 0.99)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 1/99 Liquid/Dust Inhalation Dose (mg/kg/day)

**Table G.3. Residential Handler Non-cancer Risk Estimates Assuming 50/50 Liquid/Dust Ratio Formulation Pet Collars.**

| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 50/50 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 50/50 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
|---|---|---|---|---|---|---|
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0092 | 0.00016 | 8,000 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0154 | 0.00028 | 4,800 |
| | | 0.010: 32 gram collar | | 0.0260 | 0.00046 | 2,800 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0122 | 0.00022 | 6,000 |
| | | 0.0055: 17 gram collar | | 0.0138 | 0.00025 | 5,300 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0097 | 0.00017 | 7,600 |
| | | 0.0080: 25 gram collar | | 0.0203 | 0.00036 | 3,600 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0154 | 0.00028 | 4,800 |
| | | 0.010: 32 gram collar | | 0.0260 | 0.00046 | 2,800 |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0081 | 0.00014 | 9,100 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0406 | 0.00072 | 1,800 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0183 | 0.00033 | 4,000 |
| | 11556-165: | 0.0045: | | 0.0114 | 0.00020 | 6,400 |

| Table G.3. Residential Handler Non-cancer Risk Estimates Assuming 50/50 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 50/50 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 50/50 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| | Cat | 15 gram collar | | | | |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 50/50 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.5) + (Dust dermal dose * 0.5)
4 Combined 50/50 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.5) + (Dust dermal dose * 0.5)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)

| Table G.4. Residential Handler Non-cancer Risk Estimates Assuming 99/1 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 99/1 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 99/1 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0014 | 3.27E-06 | 400,000 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0023 | 5.49E-06 | 240,000 |
| | | 0.010: 32 gram collar | | 0.0039 | 9.25E-06 | 140,000 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0018 | 4.33E-06 | 300,000 |
| | | 0.0055: 17 gram collar | | 0.0021 | 4.91E-06 | 270,000 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0015 | 3.47E-06 | 380,000 |
| | | 0.0080: 25 gram collar | | 0.0030 | 7.22E-06 | 180,000 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0023 | 5.49E-06 | 240,000 |
| | | 0.010: | | 0.0039 | 9.25E-06 | 140,000 |

| Table G.4. Residential Handler Non-cancer Risk Estimates Assuming 99/1 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 99/1 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 99/1 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| | | 32 gram collar | | | | |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0012 | 2.89E-06 | 450,000 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0061 | 1.44E-05 | 91,000 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0027 | 6.51E-06 | 200,000 |
| | 11556-165: Cat | 0.0045: 15 gram collar | | 0.0017 | 4.07E-06 | 320,000 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 99/1 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.99) + (Dust dermal dose * 0.01)
4 Combined 99/1 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.99) + (Dust dermal dose * 0.01)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| Application of TCVP Dusts/Powders | 47000-123: Dog | Inhalation: 300 | 1,700 | 3.1 | 0.00037: small | 2 animals treated per day | 0.0018 | N/A, No Dermal Hazard | 0.000034 | 39,000 |
| | | | | | 0.00094: medium | | 0.0044 | | 0.000084 | 16,000 |
| | | | | | 0.0015: large | | 0.0071 | | 0.00013 | 9,700 |
| | 47000-123: Cat | | | | 0.000094: small | | 0.00044 | | 0.0000084 | 160,000 |
| | | | | | 0.00023: medium | | 0.0011 | | 0.000020 | 65,000 |

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| | | | | | 0.00034: large | | 0.0016 | | 0.000030 | 43,000 |
| | 2596-78: Cat | | | | 0.00062: small | | 0.0029 | | 0.000056 | 24,000 |
| | | | | | 0.0010: large | | 0.0049 | | 0.000093 | 14,000 |
| | 2596-79; Dog | | | | 0.0010: small | | 0.0049 | | 0.000093 | 14,000 |
| | | | | | 0.0021: medium | | 0.0097 | | 0.00019 | 7,100 |
| | | | | | 0.0026: large | | 0.0122 | | 0.00023 | 5,600 |
| | 67517-82: Dog | | | | 0.0011: small | | 0.0053 | | 0.00010 | 13,000 |
| | | | | | 0.0028: medium | | 0.013 | | 0.00025 | 5,200 |
| | | | | | 0.0045: large | | 0.021 | | 0.00040 | 3,200 |
| | 67517-82: Cat | | | | 0.00028: small | | 0.0013 | | 0.000025 | 52,000 |
| | | | | | 0.00067: medium | | 0.0032 | | 0.000061 | 22,000 |
| | | | | | 0.0010: large | | 0.0048 | | 0.000091 | 14,000 |
| Application of TCVP Pump/Trigger Sprays | 2596-126, -140: Cat (Trigger) | | 820 | 3.3 | 0.00055: small | | 0.0013 | N/A, No Dermal Hazard | 0.000053 | 25000 |
| | | | | | 0.00077: medium | | 0.0018 | | 0.000074 | 18000 |
| | 2596-140 Cat (Pump) | | | | 0.00011: small | | 0.00026 | | 0.000011 | 120,000 |
| | | | | | 0.00016: large | | 0.00036 | | 0.000015 | 87,000 |

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| | 2596-125, -140: Dog (Trigger) | | | | 0.00077: small | | 0.0018 | | 0.000074 | 18,000 |
| | | | | | 0.00088: medium | | 0.0020 | | 0.000084 | 16,000 |
| | | | | | 0.0015: large | | 0.0035 | | 0.00015 | 8,900 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide)
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/pet) × Area Treated or Amount Handled (pets/day) × Dermal Absorption Factor (9.6 %) ÷ Body Weight (69 kg). Dermal dose presented only for purpose of calculation of cancer risks for residential handlers.
4 No dermal MOE estimated due to lack of dermal hazard.
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/pet) × Area Treated or Amount Handled (pets/day) ÷ Body Weight (69 kg).
6 Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## Appendix H. Summary of Residential Handler Cancer Exposure and Risk Estimates

**Table H.1. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 1/99 Liquid/Dust Formulation Approach.**

| Reg No./ Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | 1/99 Liquid/Dust Cancer Risk Estimate[3] |
|---|---|---|---|---|---|
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 2.2E-07 |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.7E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 6.3E-07 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 3.0E-07 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 3.3E-07 |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 2.4E-07 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 4.9E-07 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.7E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 6.3E-07 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 2.0E-07 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 9.8E-07 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 4.4E-07 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 2.8E-07 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.01) + (Dust LADD * 0.99)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table H.2. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 50/50 Liquid/Dust Formulation Approach**

| Reg No./ Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | 50/50 Liquid/Dust Cancer Risk Estimate[3] |
|---|---|---|---|---|---|
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 1.2E-07 |

| Table H.2. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 50/50 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 2.0E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 3.4E-07 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 1.6E-07 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 1.8E-07 |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 1.3E-07 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 2.7E-07 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 2.0E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 3.4E-07 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 1.1E-07 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 5.3E-07 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 2.4E-07 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 1.5E-07 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.5) + (Dust LADD * 0.5)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table H.3. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 99/1 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 1.8E-08 |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.0E-08 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 5.0E-08 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 2.3E-08 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 2.7E-08 |

| Table H.3. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 99/1 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 1.9E-08 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 3.9E-08 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.0E-08 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 5.0E-08 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 1.6E-08 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 7.8E-08 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 3.5E-08 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 2.2E-08 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.99) + (Dust LADD * 0.01)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table H.4. Residential Handler Dermal and Inhalation Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Total LADD[1,2]** | **Cancer Risk Estimate[3]** |
| **Dust/Powder** | | | | |
| 47000-123: Dog | Small | Adult | 1.9E-05 | 3.5E-08 |
| | Medium | | 4.7E-05 | 8.7E-08 |
| | Large | | 7.6E-05 | 1.4E-07 |
| 47000-123: Cat | Small | | 4.7E-06 | 8.7E-09 |
| | Medium | | 1.1E-05 | 2.1E-08 |
| | Large | | 1.7E-05 | 3.1E-08 |
| 2596-78: Cat | Small | | 3.1E-05 | 5.7E-08 |
| | Medium | | 5.2E-05 | 9.6E-08 |

| Table H.4. Residential Handler Dermal and Inhalation Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Total LADD[1,2]** | **Cancer Risk Estimate[3]** |
| 2596-79: Dog | Small | Adult | 5.2E-05 | 9.6E-08 |
| | Medium | | 1.0E-04 | 1.9E-07 |
| | Large | | 1.3E-04 | 2.4E-07 |
| 67517-82: Dog | Small | | 5.7E-05 | 1.0E-07 |
| | Medium | | 1.4E-04 | 2.6E-07 |
| | Large | | 2.3E-04 | 4.2E-07 |
| 67517-82: Cat | Small | | 1.4E-05 | 2.6E-08 |
| | Medium | | 3.4E-05 | 6.2E-08 |
| | Large | | 5.1E-05 | 9.4E-08 |
| **Pump/Trigger Sprays** | | | | |
| 2596-126: -140: Cat (Trigger) | Small | Adult | 1.4E-05 | 2.5E-08 |
| | Large | | 1.9E-05 | 3.5E-08 |
| 2596-140: Cat (Pump) | Small | | 2.8E-06 | 5.1E-09 |
| | Large | | 3.9E-06 | 7.2E-09 |
| 2596-125, -140: Dog (Trigger) | Small | | 1.9E-05 | 3.5E-08 |
| | Medium | | 2.2E-05 | 4.0E-08 |
| | Large | | 3.9E-05 | 7.0E-08 |

1 Total Lifetime Average Daily Dose (LADD, mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
2 Dermal and Inhalation LADD equations provided in Appendix B.
3 Cancer risk estimates = Total LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

## Appendix I. Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates

**Table I.1. Residential Post-application Non-cancer Incidental Oral Dose Assuming a Liquid or Dust Formulation for Pet Collars.**

| Animal Type | Animal Size | Application Rate (mg ai) | $F_{aihands}$ | DE<br>Dermal Exposure (mg) | $SA_H$<br>Surface area of 1 hand ($cm^2$) | HR<br>Hand residue loading ($mg/cm^2$) | $F_m$<br>Fraction of hand mouthed | ET<br>Exposure Time (hours/day) | Replenish-ment interval (min) | N_Replen<br># replenish-ment intervals per hour (intervals/hr) | SE<br>Fraction Saliva Extraction | Freq_HtM<br>Number of hand-to-mouth contacts events per hour (events/hr) | Incidental oral Absorbed Dose (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assume Liquid Formulation -- Use of Davis Study (2008) and Liquid TCs** | | | | | | | | | | | | | |
| Cat (2596-49) | small | 1650 | 0.04 | 6.1 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0056 |
| | medium | 1650 | 0.04 | 3.7 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0033 |
| | large | 1650 | 0.04 | 2.3 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Dog (2596-50,62) | small | 2774 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0047 |
| | large | 4672 | 0.04 | 2.4 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Cat (2596-83) | small | 1752 | 0.04 | 6.5 | 150 | 0.0009 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0059 |
| | large | 3650 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0046 |
| Cat (2596-139) | small | 1460 | 0.04 | 5.4 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0049 |
| | medium | 1460 | 0.04 | 3.2 | 150 | 0.0004 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0030 |
| | large | 1460 | 0.04 | 2.0 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0018 |
| Dog (11556-164) | small | 3288 | 0.04 | 6.1 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0055 |
| | medium | 3288 | 0.04 | 2.6 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0024 |
| | large | 3288 | 0.04 | 1.7 | 150 | 0.0002 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0015 |
| Cat (11556-165) | small | 2055 | 0.04 | 7.6 | 150 | 0.0010 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0069 |
| | medium | 2055 | 0.04 | 4.6 | 150 | 0.0006 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0042 |
| | large | 2055 | 0.04 | 2.9 | 150 | 0.0004 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0026 |
| Dog (2596-84) | small | 2774 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0047 |
| | large | 4672 | 0.04 | 2.4 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Dog (2596-139) | small | 7300 | 0.04 | 13.5 | 150 | 0.0018 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0123 |
| | medium | 7300 | 0.04 | 5.8 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0053 |
| | large | 7300 | 0.04 | 3.7 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0034 |
| Cat (2596-63) | small | 2190 | 0.04 | 8.1 | 150 | 0.0011 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0074 |
| | large | 2482 | 0.04 | 3.5 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0031 |
| **Assume Dust Formulation -- Use of Davis Study (2008) and Dust TCs** | | | | | | | | | | | | | |
| Cat (2596-49) | small | 1650 | 0.37 | 166 | 150 | 0.2049 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.40 |
| | medium | 1650 | 0.37 | 100 | 150 | 0.1229 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.84 |
| | large | 1650 | 0.37 | 62 | 150 | 0.0768 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.52 |
| Dog (2596-50,62) | small | 2774 | 0.37 | 140 | 150 | 0.1723 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.18 |
| | large | 4672 | 0.37 | 64 | 150 | 0.0791 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.54 |
| Cat (2596-83) | small | 1752 | 0.37 | 176 | 150 | 0.2176 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.48 |

**Table I.1. Residential Post-application Non-cancer Incidental Oral Dose Assuming a Liquid or Dust Formulation for Pet Collars.**

| Animal Type | Animal Size | Application Rate (mg ai) | $F_{aihands}$ | DE<br>Dermal Exposure (mg) | $SA_H$<br>Surface area of 1 hand ($cm^2$) | HR<br>Hand residue loading ($mg/cm^2$) | $F_m$<br>Fraction of hand mouthed | ET<br>Exposure Time (hours/day) | Replenish-ment interval (min) | N_Replen<br># replenish-ment intervals per hour (intervals/hr) | SE<br>Fraction Saliva Extraction | Freq_HtM<br>Number of hand-to-mouth contacts events per hour (events/hr) | Incidental oral Absorbed Dose (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | large | 3650 | 0.37 | 138 | 150 | 0.1700 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.16 |
| Cat (2596-139) | small | 1460 | 0.37 | 147 | 150 | 0.1813 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.24 |
| | medium | 1460 | 0.37 | 88 | 150 | 0.1088 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.74 |
| | large | 1460 | 0.37 | 55 | 150 | 0.0680 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.46 |
| Dog (11556-164) | small | 3288 | 0.37 | 166 | 150 | 0.2042 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.39 |
| | medium | 3288 | 0.37 | 71 | 150 | 0.0875 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.60 |
| | large | 3288 | 0.37 | 45 | 150 | 0.0557 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.38 |
| Cat (11556-165) | small | 2055 | 0.37 | 207 | 150 | 0.2552 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.74 |
| | medium | 2055 | 0.37 | 124 | 150 | 0.1531 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.04 |
| | large | 2055 | 0.37 | 78 | 150 | 0.0957 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.65 |
| Dog (2596-84) | small | 2774 | 0.37 | 140 | 150 | 0.1723 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.18 |
| | large | 4672 | 0.37 | 64 | 150 | 0.0791 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.54 |
| Dog (2596-139) | small | 7300 | 0.37 | 368 | 150 | 0.4533 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 3.09 |
| | medium | 7300 | 0.37 | 158 | 150 | 0.1943 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.33 |
| | large | 7300 | 0.37 | 100 | 150 | 0.1236 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.84 |
| Cat (2596-63) | small | 2190 | 0.37 | 221 | 150 | 0.2720 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.86 |
| | large | 2482 | 0.37 | 94 | 150 | 0.1156 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.79 |

1. Application rates are label defined. Refer to D426984.
2. Dermal Exposure (mg/day) = [Transfer Coefficient ($cm^2$/hr)] * [Application Rate (label defined) * Fraction Application Rate (0.0040; Davis, M. Et. al) ÷ Surface Area of Cat/Dog (Cat: Small, 1,500; Medium, 2,500; Large, 4,000 $cm^2$ - Dog: Small, 3,000; Medium, 7,000; Large, 11,000 $cm^2$)] x [Exposure Time (Adults, 0.77 hours/day; Children, 1.0 hours/day))
3. Incidental Oral Dose (mg/kg/day) = [Hand Residue Loading ($mg/cm^2$)] × [Fraction of Hand Mouthed (0.13) × Surface Area of 1 Child Hand (150 $cm^2$ )] x [Exposure Time (1.0 hrs/day) × # of Replenishment Intervals/hr (4 int/hr)) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (20 events/hr) ) ÷ ( # of Replenishment Intervals/hr))] / [Body Weight (11 kg child 1 to < 2 years old years old)]
   Where the Hand Residue Loading ($mg/cm^2$) = [$Fai_{hands}$ (Solid, 0.37; Liquids; 0.040) x Dermal Exposure (mg/day)] ÷ [Surface Area of 1 Child Hand (150 $cm^2$) x 2]

| Table I.2. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 1/99 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 1/99 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **2** |
| | | | Medium | 0.00334 | 0.83861 | **3.4** |
| | | | Large | 0.00209 | 0.52413 | **5.4** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **2.4** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **5.2** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **1.9** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **2.4** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **2.3** |
| | | | Medium | 0.00296 | 0.74213 | **3.8** |
| | | | Large | 0.00185 | 0.46383 | **6.1** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **2** |
| | | | Medium | 0.00238 | 0.59690 | **4.7** |
| | | | Large | 0.00151 | 0.37985 | **7.4** |
| 11556-165: Cat | Children 1 < 2 | 2,060 | Small | 0.00693 | 1.74096 | **1.6** |
| | | | Medium | 0.00416 | 1.04458 | **2.7** |
| | | | Large | 0.00260 | 0.65286 | **4.3** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **2.4** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **5.2** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **0.91** |
| | | | Medium | 0.00528 | 1.32524 | **2.1** |
| | | | Large | 0.00336 | 0.84333 | **3.4** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **1.5** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **3.6** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.01) + (Dust HtM Dose * 0.99)]. Bolded MOEs indicate a risk of concern.

| Table I.3. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 50/50 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 50/50 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **4** |
| | | | Medium | 0.00334 | 0.83861 | **6.7** |
| | | | Large | 0.00209 | 0.52413 | **11** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **4.7** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **10** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **3.8** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **4.8** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **4.5** |
| | | | Medium | 0.00296 | 0.74213 | **7.5** |
| | | | Large | 0.00185 | 0.46383 | **12** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **4** |
| | | | Medium | 0.00238 | 0.59690 | **9.3** |
| | | | Large | 0.00151 | 0.37985 | **15** |
| 11556-165: Cat | Children | 2,060 | Small | 0.00693 | 1.74096 | **3.2** |

| Table I.3. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 50/50 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 50/50 Liquid/Dust Combined MOE[4] |
| | 1 < 2 | | Medium | 0.00416 | 1.04458 | **5.3** |
| | | | Large | 0.00260 | 0.65286 | **8.5** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **4.7** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **10** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **1.8** |
| | | | Medium | 0.00528 | 1.32524 | **4.2** |
| | | | Large | 0.00336 | 0.84333 | **6.6** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **3** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **7.1** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.5) + (Dust HtM Dose * 0.5)]. Bolded MOEs indicate a risk of concern.

| Table I.4. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 99/1 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 99/1 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **140** |
| | | | Medium | 0.00334 | 0.83861 | **240** |
| | | | Large | 0.00209 | 0.52413 | **380** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **170** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **370** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **140** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **170** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **160** |
| | | | Medium | 0.00296 | 0.74213 | **270** |
| | | | Large | 0.00185 | 0.46383 | **430** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **140** |
| | | | Medium | 0.00238 | 0.59690 | **340** |
| | | | Large | 0.00151 | 0.37985 | **530** |
| 11556-165: Cat | Children 1 < 2 | 2,060 | Small | 0.00693 | 1.74096 | **120** |
| | | | Medium | 0.00416 | 1.04458 | **190** |
| | | | Large | 0.00260 | 0.65286 | **310** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **170** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **370** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **65** |
| | | | Medium | 0.00528 | 1.32524 | **150** |
| | | | Large | 0.00336 | 0.84333 | **240** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **110** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **250** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.99) + (Dust HtM Dose * 0.01)]. Bolded MOEs indicate a risk of concern.

| Table I.5. Residential Post-Application Non-Cancer Exposure and Risk Estimates from TCVP Dust/Powder and Pump/Trigger Spray Formulations. Incidental Oral LOC is an MOE = 1,000 | | | | | | |
|---|---|---|---|---|---|---|
| **EPA Reg. No./ Animal** | **Lifestage** | **Application Rate (mg ai)[1]** | **Animal Size** | **Dermal Exposure (mg/day)[2]** | **Incidental Oral Dose (mg/kg/day)[3]** | **MOE[4]** |
| **Dusts/Powders** | | | | | | |
| 47000-123: Dog | Children 1 < 2 | 170 | Small | 1.0 | 0.0087 | **320** |
| | | 430 | Medium | 1.1 | 0.0093 | **300** |
| | | 680 | Large | 1.1 | 0.0095 | **300** |
| 47000-123: Cat | Children 1 < 2 | 43 | Small | 0.52 | 0.0043 | **640** |
| | | 100 | Medium | 0.74 | 0.0063 | **450** |
| | | 150 | Large | 0.70 | 0.0059 | **480** |
| 2596-78: Cat | Children 1 < 2 | 280 | Small | 3.4 | 0.0287 | **98** |
| | | 470 | Large | 2.1 | 0.0180 | **160** |
| 2596-79: Dog | Children 1 < 2 | 470 | Small | 2.9 | 0.0240 | **120** |
| | | 940 | Medium | 2.4 | 0.0205 | **140** |
| | | 1,200 | Large | 1.9 | 0.0163 | **170** |
| 67517-82: Dog | Children 1 < 2 | 510 | Small | 3.1 | 0.0261 | **110** |
| | | 1,300 | Medium | 3.3 | 0.0280 | **100** |
| | | 2,000 | Large | 3.4 | 0.0285 | **98** |
| 67517-82: Cat | Children 1 < 2 | 130 | Small | 1.6 | 0.0130 | **210** |
| | | 310 | Medium | 2.2 | 0.0188 | **150** |
| | | 460 | Large | 2.1 | 0.0176 | **160** |
| **Pump/Trigger Sprays** | | | | | | |
| 2596-126, 140: Cat (Trigger) | Children 1 < 2 | 250 | Small | 1.9 | 0.00172 | 1,600 |
| | | 350 | Large | 0.99 | 0.00090 | 3,100 |
| 2596-140: Cat (Pump) | Children 1 < 2 | 51 | Small | 0.39 | 0.00035 | 8,000 |
| | | 71 | Large | 0.20 | 0.00018 | 15,000 |
| 2596-125, -140: Dog (Trigger) | Children 1 < 2 | 350 | Small | 1.3 | 0.00120 | 2,300 |
| | | 400 | Medium | 0.65 | 0.00059 | 4,800 |
| | | 700 | Large | 0.72 | 0.00066 | 4,300 |

1. Application rates are label defined. Refer to D426984.
2. Dermal Exposure (mg/day) = [Transfer Coefficient ($cm^2$/hr)] * [Application Rate (label defined) * Fraction Application Rate (Dust, 0.00048; Spray, 0.0081) ÷ Surface Area of Cat/Dog (Cat: Small, 1,500; Medium, 2,500; Large, 4,000 $cm^2$ - Dog: Small, 3,000; Medium, 7,000; Large, 11,000 $cm^2$)] x [Exposure Time (Adults, 0.77 hours/day; Children, 1.0 hours/day))]
3. Incidental Oral Dose (mg/kg/day) = [Hand Residue Loading (mg/$cm^2$)] × [Fraction of Hand Mouthed (0.13) × Surface Area of 1 Child Hand (150 $cm^2$ )] x [Exposure Time (1.0 hrs/day) × # of Replenishment Intervals/hr (4 int/hr)) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (20 events/hr) ) ÷ ( # of Replenishment Intervals/hr))] / [Body Weight (11 kg child 1 to < 2 years old years old)]
   Where the Hand Residue Loading (mg/$cm^2$) = [$Fai_{hands}$ (Dusts, 0.37; Liquids; 0.040) x Dermal Exposure (mg/day)] ÷ [Surface Area of 1 Child Hand (150 $cm^2$) x 2]
4. MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ Incidental Oral Dose (mg/kg/day). Bolded MOEs indicate a risk of concern.

## Appendix J. Summary of Residential Post-Application Cancer Exposure and Risks

| Table J.1. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar – 1/99 Ratio of Liquid/Dust Formulation | | | | | | |
|---|---|---|---|---|---|---|
| **Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **Combined 1/99 Liquid/Dust LADD[3]** | **Cancer Risk Estimate[4]** |
| **Exposure Data Source: Davis, M., et al (2008)** | | | | | | |
| 2596-49: Cat | Small | Adult | 5.8E-03 | 1.6E-01 | 1.5E-01 | 2.8E-04 |
| | Medium | | 3.5E-03 | 9.4E-02 | 9.3E-02 | 1.7E-04 |
| | Large | | 2.2E-03 | 5.8E-02 | 5.8E-02 | 1.1E-04 |
| 2596-50,62: Dog | Small | | 4.9E-03 | 1.3E-01 | 1.3E-01 | 2.4E-04 |
| | Large | | 2.2E-03 | 6.0E-02 | 6.0E-02 | 1.1E-04 |
| 2596-83: Cat | Small | | 6.2E-03 | 1.7E-01 | 1.6E-01 | 3.0E-04 |
| | Large | | 4.8E-03 | 1.3E-01 | 1.3E-01 | 2.3E-04 |
| 2596-139: Cat | Small | | 5.1E-03 | 1.4E-01 | 1.4E-01 | 2.5E-04 |
| | Medium | | 3.1E-03 | 8.3E-02 | 8.2E-02 | 1.5E-04 |
| | Large | | 1.9E-03 | 5.2E-02 | 5.1E-02 | 9.4E-05 |
| 11556-164: Dog | Small | | 5.8E-03 | 1.6E-01 | 1.5E-01 | 2.8E-04 |
| | Medium | | 2.5E-03 | 6.7E-02 | 6.6E-02 | 1.2E-04 |
| | Large | | 1.6E-03 | 4.2E-02 | 4.2E-02 | 7.7E-05 |
| 11556-165: Cat | Small | | 7.2E-03 | 1.9E-01 | 1.9E-01 | 3.5E-04 |
| | Medium | | 4.3E-03 | 1.2E-01 | 1.2E-01 | 2.1E-04 |
| | Large | | 2.7E-03 | 7.3E-02 | 7.2E-02 | 1.3E-04 |
| 2596-84: Dog | Small | | 4.9E-03 | 1.3E-01 | 1.3E-01 | 2.4E-04 |
| | Large | | 2.2E-03 | 6.0E-02 | 6.0E-02 | 1.1E-04 |
| 2596-139: Dog | Small | | 1.3E-02 | 3.5E-01 | 3.4E-01 | 6.3E-04 |
| | Medium | | 5.5E-03 | 1.5E-01 | 1.5E-01 | 2.7E-04 |
| | Large | | 3.5E-03 | 9.4E-02 | 9.3E-02 | 1.7E-04 |
| 2596-63: Cat | Small | | 7.7E-03 | 2.1E-01 | 2.1E-01 | 3.8E-04 |
| | Large | | 3.3E-03 | 8.8E-02 | 8.7E-02 | 1.6E-04 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 1/99 Liquid/Dust LADD = (Liquid LADD * 0.01) + (Dust LADD * 0.99)

4 Cancer risk estimates = Combined 1/99 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table J.2. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar - 50/50 Ratio of Liquid and Solid Formulation**

| Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | Combined 50/50 Liquid/Dust LADD[3] | Cancer Risk Estimate[4] |
|---|---|---|---|---|---|---|
| 2596-49: Cat | Small | Adult | 2.9E-03 | 7.8E-02 | 8.1E-02 | 1.5E-04 |
| | Medium | | 1.7E-03 | 4.7E-02 | 4.9E-02 | 8.9E-05 |
| | Large | | 1.1E-03 | 2.9E-02 | 3.0E-02 | 5.5E-05 |
| 2596-50,62: Dog | Small | | 2.4E-03 | 6.6E-02 | 6.8E-02 | 1.2E-04 |
| | Large | | 1.1E-03 | 3.0E-02 | 3.1E-02 | 5.7E-05 |
| 2596-83: Cat | Small | | 3.1E-03 | 8.3E-02 | 8.6E-02 | 1.6E-04 |
| | Large | | 2.4E-03 | 6.5E-02 | 6.7E-02 | 1.2E-04 |
| 2596-139: Cat | Small | | 2.6E-03 | 6.9E-02 | 7.2E-02 | 1.3E-04 |
| | Medium | | 1.5E-03 | 4.1E-02 | 4.3E-02 | 7.9E-05 |
| | Large | | 9.6E-04 | 2.6E-02 | 2.7E-02 | 4.9E-05 |
| 11556-164: Dog | Small | | 2.9E-03 | 7.8E-02 | 8.1E-02 | 1.5E-04 |
| | Medium | | 1.2E-03 | 3.3E-02 | 3.5E-02 | 6.3E-05 |
| | Large | | 7.9E-04 | 2.1E-02 | 2.2E-02 | 4.0E-05 |
| 11556-165: Cat | Small | | 3.6E-03 | 9.7E-02 | 1.0E-01 | 1.8E-04 |
| | Medium | | 2.2E-03 | 5.8E-02 | 6.0E-02 | 1.1E-04 |
| | Large | | 1.4E-03 | 3.6E-02 | 3.8E-02 | 6.9E-05 |
| 2596-84: Dog | Small | | 2.4E-03 | 6.6E-02 | 6.8E-02 | 1.2E-04 |
| | Large | | 1.1E-03 | 3.0E-02 | 3.1E-02 | 5.7E-05 |
| 2596-139: Dog | Small | | 6.4E-03 | 1.7E-01 | 1.8E-01 | 3.3E-04 |
| | Medium | | 2.7E-03 | 7.4E-02 | 7.7E-02 | 1.4E-04 |
| | Large | | 1.7E-03 | 4.7E-02 | 4.9E-02 | 8.9E-05 |
| 2596-63: Cat | Small | | 3.8E-03 | 1.0E-01 | 1.1E-01 | 2.0E-04 |
| | Large | | 1.6E-03 | 4.4E-02 | 4.6E-02 | 8.3E-05 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 50/50 Liquid/Dust LADD = (Liquid LADD * 0.5) + (Dust LADD * 0.5)

4 Cancer risk estimates = Combined 50/50 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ (mg/kg/day)$^{-1}$

**Table J.3. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar - 99/1 Ratio of Liquid and Solid Formulation**

| Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | Combined 99/1 Liquid/Dust LADD[3] | Cancer Risk Estimate[4] |
|---|---|---|---|---|---|---|
| 2596-49: Cat | Small | Adult | 5.7E-03 | 1.6E-03 | 7.3E-03 | 1.3E-05 |
| | Medium | | 3.4E-03 | 9.4E-04 | 4.4E-03 | 8.0E-06 |
| | Large | | 2.2E-03 | 5.8E-04 | 2.7E-03 | 5.0E-06 |
| 2596-50,62: Dog | Small | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| | Large | | 2.2E-03 | 6.0E-04 | 2.8E-03 | 5.2E-06 |
| 2596-83: Cat | Small | | 6.1E-03 | 1.7E-03 | 7.7E-03 | 1.4E-05 |
| | Large | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| 2596-139: Cat | Small | | 5.1E-03 | 1.4E-03 | 6.5E-03 | 1.2E-05 |
| | Medium | | 3.0E-03 | 8.3E-04 | 3.9E-03 | 7.1E-06 |
| | Large | | 1.9E-03 | 5.2E-04 | 2.4E-03 | 4.4E-06 |
| 11556-164: Dog | Small | | 5.7E-03 | 1.6E-03 | 7.3E-03 | 1.3E-05 |
| | Medium | | 2.4E-03 | 6.7E-04 | 3.1E-03 | 5.7E-06 |
| | Large | | 1.6E-03 | 4.2E-04 | 2.0E-03 | 3.6E-06 |
| 11556-165: Cat | Small | | 7.1E-03 | 1.9E-03 | 9.1E-03 | 1.7E-05 |
| | Medium | | 4.3E-03 | 1.2E-03 | 5.5E-03 | 1.0E-05 |
| | Large | | 2.7E-03 | 7.3E-04 | 3.4E-03 | 6.2E-06 |
| 2596-84: Dog | Small | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| | Large | | 2.2E-03 | 6.0E-04 | 2.8E-03 | 5.2E-06 |
| 2596-139: Dog | Small | | 1.3E-02 | 3.5E-03 | 1.6E-02 | 3.0E-05 |
| | Medium | | 5.4E-03 | 1.5E-03 | 6.9E-03 | 1.3E-05 |
| | Large | | 3.5E-03 | 9.4E-04 | 4.4E-03 | 8.1E-06 |
| 2596-63: Cat | Small | | 7.6E-03 | 2.1E-03 | 9.7E-03 | 1.8E-05 |
| | Large | | 3.2E-03 | 8.8E-04 | 4.1E-03 | 7.5E-06 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 99/1 Liquid/Dust LADD = (Liquid LADD * 0.99) + (Dust LADD * 0.01)

4 Cancer risk estimates = Combined 99/1 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ (mg/kg/day)$^{-1}$

| Table J.4. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Animal Type** | **Animal Size** | **Lifestage** | **LADD[1,2]** | **Cancer Risk Estimate[3]** |
| **Dust/Powder** | | | | |
| 47000-123: Dog | Small | Adult | 5.9E-04 | 1.1E-06 |
| | Medium | | 6.3E-04 | 1.2E-06 |
| | Large | | 6.4E-04 | 1.2E-06 |
| 47000-123: Cat | Small | | 2.9E-04 | 5.4E-07 |
| | Medium | | 4.2E-04 | 7.8E-07 |
| | Large | | 4.0E-04 | 7.3E-07 |
| 2596-78: Cat | Small | | 1.9E-03 | 3.6E-06 |
| | Large | | 1.2E-03 | 2.2E-06 |
| 2596-79: Dog | Small | | 1.6E-03 | 3.0E-06 |
| | Medium | | 1.4E-03 | 2.5E-06 |
| | Large | | 1.1E-03 | 2.0E-06 |
| 67517-82: Dog | Small | | 1.8E-03 | 3.2E-06 |
| | Medium | | 1.9E-03 | 3.5E-06 |
| | Large | | 1.9E-03 | 3.5E-06 |
| 67517-82: Cat | Small | | 8.8E-04 | 1.6E-06 |
| | Medium | | 1.3E-03 | 2.3E-06 |
| | Large | | 1.2E-03 | 2.2E-06 |
| **Pump/Trigger Spray** | | | | |
| 2596-126, 140: Cat (Trigger) | Small | Adult | 5.3E-04 | 9.6E-07 |
| | Large | | 2.8E-04 | 5.1E-07 |
| 2596-140: Cat (Pump) | Small | | 1.1E-04 | 2.0E-07 |
| | Large | | 5.6E-05 | 1.0E-07 |
| 2596-125, -140: Dog (Trigger) | Small | | 3.7E-04 | 6.7E-07 |
| | Medium | | 1.8E-04 | 3.3E-07 |
| | Large | | 2.0E-04 | 3.7E-07 |

1 Total Lifetime Average Daily Dose (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
2 Dermal and Inhalation LADD equations provided in Appendix B.
3 Cancer risk estimates = Total LADD × Q1*, where Q1* = $1.83 \times 10^{-3}$ (mg/kg/day)$^{-1}$

## Appendix K. Summary of Occupational Handler Non-Cancer Exposures and Risks



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| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Floors) | 0.00077 lb ai/sq ft | 100,000 (sq ft/day) | 2.5E-04 | 4.9E-05 | 2.5E-05 | 9.3E-05 | 16,000 | 81,000 | 160,000 | 43,000 |
| | Poultry Buildings (Floor Management, Fowl Tick) | 0.00064 lb ai/sq ft | | 2.0E-04 | 4.1E-05 | 2.0E-05 | 7.7E-05 | 19,000 | 97,000 | 190,000 | 51,000 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 4.1E-05 | 8.3E-06 | 4.1E-06 | 1.6E-05 | 95,000 | 480,000 | 950,000 | 250,000 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 2.0E-05 | 4.1E-06 | 2.0E-06 | 7.7E-06 | 190,000 | 970,000 | 1,900,000 | 510,000 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 4.9E-07 | 9.8E-08 | 4.9E-08 | 1.9E-07 | 8.1E+06 | 4.0E+07 | 8.1E+07 | 2.1E+07 |
| | | 0.064 lb ai/gallon | | 4.1E-07 | 8.1E-08 | 4.1E-08 | 1.5E-07 | 9.7E+06 | 4.8E+07 | 9.7E+07 | 2.6E+07 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick) | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.050 | 0.010 | 0.0050 | 0.00028 | **79** | 400 | 790 | 14,000 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 0.020 | 0.040 | 0.0020 | 0.00011 | **200** | 990 | 2,000 | 35,000 |
| (2b) Mixing/ Loading Wettable Powders for Paint Applications | Poultry (Floor Management – Roost) | 0.080 lb ai/gallon | 2 gallons | 1.0E-04 | 2.0E-05 | 1.0E-05 | 5.6E-07 | 40,000 | 200,000 | 400,000 | 7,100,000 |
| (3a) Mixing/ Loading Dusts for | | 0.030 lb ai/gallon | | 3.7E-05 | 7.5E-06 | 3.7E-06 | 2.1E-07 | 110,000 | 530,000 | 1,100,000 | 1.9E+07 |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Paint Applications (WP Data as Surrogate) | | | | | | | | | | | |
| **Applicators** | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 3.9E-04 | 7.9E-05 | 3.9E-05 | 5.0E-05 | 10,000 | 50,000 | 100,000 | 79,000 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 3.8E-04 | 7.6E-05 | 3.8E-05 | 4.8E-05 | 10,000 | 52,000 | 100,000 | 82,000 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3.2E-04 | 6.3E-05 | 3.2E-05 | 4.0E-05 | 12,000 | 63,000 | 120,000 | 99,000 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 1.6E-04 | 3.2E-05 | 1.6E-05 | 2.0E-05 | 25,000 | 120,000 | 250,000 | 200,000 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 6.4E-05 | 1.3E-05 | 6.4E-06 | 8.1E-06 | 61,000 | 310,000 | 610,000 | 490,000 |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 3.2E-05 | 6.3E-06 | 3.2E-06 | 4.0E-06 | 120,000 | 630,000 | 1,200,000 | 990,000 |
| (5) Open Pour Liquid Additive for | Cattle Feed (Concentrate) | 0.0039 lb ai/animal | 1,000 cows | 1.2E-05 | 2.5E-06 | 1.2E-06 | No Data | 320,000 | 1,600,000 | 3,200,000 | No Data |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 7.0E-06 | 1.4E-06 | 7.0E-07 | No Data | 560,000 | 2,800,000 | 5,600,000 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Feed Through Applications | Horse Feed | 0.0017 lb ai/animal | 500 horses | 2.7E-06 | 5.4E-07 | 2.7E-07 | No Data | 1,500,000 | 7,300,000 | 15,000,000 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 1.2E-05 | 2.4E-06 | 1.2E-06 | No Data | 330,000 | 1,700,000 | 3,300,000 | No Data |
| (6a) RTU Pet Collars - 1/99 liquid/dust ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 0.0072 | 0.0014 | 0.00072 | No Data | 550 | 2,700 | 5,500 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.012 | 0.0025 | 0.0012 | No Data | 320 | 1,600 | 3,200 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.020 | 0.0040 | 0.0020 | No Data | **200** | 980 | 2,000 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.0096 | 0.0019 | 0.00096 | No Data | 410 | 2,100 | 4,100 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.011 | 0.0022 | 0.0011 | No Data | 360 | 1,800 | 3,600 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.0078 | 0.0016 | 0.00078 | No Data | 500 | 2,500 | 5,000 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.016 | 0.0032 | 0.0016 | No Data | **250** | 1,200 | 2,500 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.012 | 0.0025 | 0.0012 | No Data | 320 | 1,600 | 3,200 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.020 | 0.0040 | 0.0020 | No Data | **200** | 980 | 2,000 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.0064 | 0.0013 | 0.00064 | No Data | 610 | 3,100 | 6,100 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.032 | 0.0064 | 0.0032 | No Data | **120** | 610 | 1,200 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.014 | 0.0029 | 0.0014 | No Data | **270** | 1,400 | 2,700 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.0090 | 0.0018 | 0.00090 | No Data | 440 | 2,200 | 4,400 | No Data |
| (6b) RTU Pet Collars - 50/50 | Cat (2596-49) | 0.0036 lb ai/animal | | 0.0037 | 0.00073 | 0.00037 | No Data | 1,100 | 5,400 | 11,000 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.0062 | 0.0012 | 0.00062 | No Data | 640 | 3,200 | 6,400 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| liquid/dust ratio | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.010 | 0.0020 | 0.0010 | No Data | 390 | 1,900 | 3,900 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.0049 | 0.00097 | 0.00049 | No Data | 810 | 4,100 | 8,100 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 700 | 3,500 | 7,000 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.0040 | 0.00079 | 0.00040 | No Data | 1,000 | 5,000 | 10,000 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.0081 | 0.0016 | 0.00081 | No Data | 490 | 2,400 | 4,900 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.0062 | 0.0012 | 0.00062 | No Data | 640 | 3,200 | 6,400 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.010 | 0.0020 | 0.0010 | No Data | 390 | 1,900 | 3,900 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.0032 | 0.00065 | 0.00032 | No Data | 1,200 | 6,100 | 12,000 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.016 | 0.0032 | 0.0016 | No Data | **240** | 1,200 | 2,400 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.0073 | 0.001465 | 0.00073 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.0046 | 0.00092 | 0.00046 | No Data | 860 | 4,300 | 8,600 | No Data |
| (6c) RTU Pet Collars - 99/1 liquid/dust ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 0.000073 | 0.000015 | 0.0000073 | No Data | 54,000 | 270,000 | 540,000 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.00012 | 0.000025 | 0.000012 | No Data | 32,000 | 160,000 | 320,000 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.00020 | 0.000041 | 0.000020 | No Data | 19,000 | 97,000 | 190,000 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.000097 | 0.000019 | 0.000010 | No Data | 40,000 | 200,000 | 400,000 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.00011 | 0.000022 | 0.000011 | No Data | 35,000 | 180,000 | 350,000 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.000079 | 0.000016 | 0.0000079 | No Data | 50,000 | 250,000 | 500,000 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Inhalation Dose (mg/kg/day) | | | | Inhalation MOEs (LOC is an MOE = 300) For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | No R | PF5 R | PF10 R | EC | No R | PF5 R | PF10 R | EC |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.00016 | 0.000033 | 0.000016 | No Data | 24,000 | 120,000 | 240,000 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.00012 | 0.000025 | 0.000012 | No Data | 32,000 | 160,000 | 320,000 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.00020 | 0.000041 | 0.000020 | No Data | 19,000 | 97,000 | 190,000 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.000065 | 0.000013 | 0.0000065 | No Data | 61,000 | 300,000 | 610,000 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.00033 | 0.000065 | 0.000033 | No Data | 12,000 | 61,000 | 120,000 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.00015 | 0.000029 | 0.000015 | No Data | 27,000 | 130,000 | 270,000 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.000091 | 0.000018 | 0.0000091 | No Data | 43,000 | 220,000 | 430,000 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 0.00075 | 0.00015 | 0.000075 | No Data | 5,200 | 26,000 | 52,000 | 5,200 |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 0.0019 | 0.00038 | 0.00019 | No Data | 2,100 | 10,000 | 21,000 | 2,100 |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 0.0030 | 0.00061 | 0.00030 | No Data | 1,300 | 6,500 | 13,000 | 1,300 |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 0.00018 | 0.000037 | 0.000018 | No Data | 22,000 | 110,000 | 220,000 | 22,000 |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 0.00045 | 0.000089 | 0.000045 | No Data | 8,800 | 44,000 | 88,000 | 8,800 |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 0.00069 | 0.00014 | 0.000069 | No Data | 5,700 | 29,000 | 57,000 | 5,700 |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 0.0013 | 0.00025 | 0.00013 | No Data | 3,100 | 16,000 | 31,000 | 3,100 |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | 1,900 |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | No Data |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 0.0043 | 0.00085 | 0.00043 | No Data | 920 | 4,600 | 9,200 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 0.0053 | 0.0011 | 0.00053 | No Data | 750 | 3,700 | 7,500 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 0.0022 | 0.00045 | 0.00022 | No Data | 1,800 | 8,800 | 18,000 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 0.0057 | 0.0011 | 0.00057 | No Data | 690 | 3,500 | 6,900 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 0.0091 | 0.0018 | 0.00091 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 0.00057 | 0.00011 | 0.000057 | No Data | 6,900 | 35,000 | 69,000 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 0.0014 | 0.00027 | 0.00014 | No Data | 2,900 | 14,000 | 29,000 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 0.00021 | 0.000042 | 0.000021 | No Data | 19,000 | 94,000 | 190,000 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 0.00029 | 0.000059 | 0.000029 | No Data | 13,000 | 67,000 | 130,000 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 0.000042 | 0.0000084 | 0.0000042 | No Data | 94,000 | 470,000 | 940,000 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 0.000061 | 0.000012 | 0.0000061 | No Data | 64,000 | 320,000 | 640,000 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 0.00029 | 0.000059 | 0.000029 | No Data | 13,000 | 67,000 | 130,000 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 0.00034 | 0.000067 | 0.000034 | No Data | 12,000 | 58,000 | 120,000 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 0.00057 | 0.00012 | 0.000057 | No Data | 6,900 | 34,000 | 69,000 | No Data |
| **Mixers/Loaders/Applicators** | | | | | | | | | | | |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.0068 | 0.0014 | 0.00068 | No Data | 580 | 2,900 | 5,800 | No Data |
| | | 0.032 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Woody Borders of Kennels, Yards, | 0.032 lb ai/sq ft | 1,000 sq ft | 0.014 | 0.0028 | 0.0014 | No Data | **280** | 1,400 | 2,800 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Campgrounds, Recreational Parks, Footpaths and Roadways | | (spot) | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 0.0045 | 0.00090 | 0.00045 | No Data | 870 | 4,400 | 8,700 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 0.0085 | 0.0017 | 0.00085 | No Data | 460 | 2,300 | 4,600 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 0.00085 | 0.00017 | 0.000085 | No Data | 4,600 | 23,000 | 46,000 | No Data |
| | | 0.0013 lb ai/animal | | 0.00023 | 0.000045 | 0.000023 | No Data | 17,000 | 87,000 | 170,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.0067 | 0.0013 | 0.00067 | No Data | 590 | 2,900 | 5,900 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0011 | 0.00023 | 0.00011 | No Data | 3,500 | 17,000 | 35,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.00068 | 0.00014 | 0.000068 | No Data | 5,800 | 29,000 | 58,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.00056 | 0.00011 | 0.000056 | No Data | 7,100 | 35,000 | 71,000 | No Data |
| (9b) Liquid: Manually-Pressurized Handwand | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.0068 | 0.0014 | 0.00068 | No Data | 580 | 2,900 | 5,800 | No Data |
| | | 0.032 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 0.0139 | 0.0028 | 0.0014 | No Data | **280** | 1,400 | 2,800 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Recreational Parks, Footpaths and Roadways | | | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 0.0045 | 0.00090 | 0.00045 | No Data | 870 | 4,400 | 8,700 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 0.0085 | 0.0017 | 0.00085 | No Data | 460 | 2,300 | 4,600 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 0.00085 | 0.00017 | 0.000085 | No Data | 4,600 | 23,000 | 46,000 | No Data |
| | | 0.0013 lb ai/animal | | 0.00023 | 0.00045 | 0.000023 | No Data | 17,000 | 87,000 | 170,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.0067 | 0.0013 | 0.00067 | No Data | 590 | 2,900 | 5,900 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0028 | 0.00054 | 0.00027 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0011 | 0.00023 | 0.00011 | No Data | 3,500 | 17,000 | 35,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.00068 | 0.00014 | 0.000068 | No Data | 5,800 | 29,000 | 58,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.00056 | 0.00011 | 0.000056 | No Data | 7,100 | 35,000 | 71,000 | No Data |
| (9c) Liquid: Mechanically -Pressurized Handgun | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.018 | 0.0036 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | | 0.032 lb ai/animal | | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, | 0.026 lb ai/animal | | 0.012 | 0.0024 | 0.0012 | No Data | 330 | 1,700 | 3,300 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Footpaths and Roadways | | | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 0.023 | 0.0045 | 0.0023 | No Data | **180** | 880 | 1,800 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 0.0023 | 0.00045 | 0.00023 | No Data | 1,800 | 8,800 | 18,000 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 0.00060 | 0.00012 | 0.000060 | No Data | 6,600 | 33,000 | 66,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.018 | 0.0035 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0073 | 0.0015 | 0.00073 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0030 | 0.00060 | 0.00023 | No Data | 1,300 | 6,600 | 13,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.0018 | 0.00036 | 0.00018 | No Data | 2,200 | 11,000 | 22,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.0015 | 0.00029 | 0.00015 | No Data | 2,700 | 13,000 | 27,000 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 (gallons/ day) | 1.2E-05 | 2.5E-06 | 1.2E-06 | No Data | 320,000 | 1,600,000 | 3,200,000 | No Data |
| | | 0.064 lb ai/gallon | | 1.0E-05 | 2.0E-06 | 1.0E-06 | No Data | 390,000 | 1,900,000 | 3,900,000 | No Data |
| (10a) Wettable Powder: Backpack Sprayer | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Poultry (Floor Management Litter, | 0.00080 lb ai/sq ft | 20,000 sq ft | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | | 0.0014 | 0.00028 | 0.00014 | No Data | 2,800 | 14,000 | 28,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 0.00070 | 0.00014 | 0.000070 | No Data | 5,700 | 28,000 | 57,000 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 0.000017 | 0.0000035 | 0.0000017 | No Data | 230,000 | 1,100,000 | 2,300,000 | No Data |
| (10b) Wettable Powder: Manually-Pressurized Handwand | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure | 0.00080 lb ai/sq ft | 20,000 sq ft | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0014 | 0.00028 | 0.00014 | No Data | 2,800 | 14,000 | 28,000 | No Data |
| | | 0.000080 lb ai/sq ft | | 0.00070 | 0.00014 | 0.000070 | No Data | 5,700 | 28,000 | 57,000 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 0.000017 | 0.0000035 | 0.0000017 | No Data | 230,000 | 1,100,000 | 2,300,000 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 4.13 | 0.828 | 0.413 | No Data | **1** | **5** | **10** | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 10.10 | 2.010 | 1.010 | No Data | **0** | **2** | **4** | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 2.97 | 0.594 | 0.297 | No Data | **1** | **7** | **13** | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - Plunger Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 0.11 | 0.023 | 0.011 | No Data | **35** | **180** | 350 | No Data |
| (10f) Wettable Powder: Plunger | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 0.039 | 0.0078 | 0.0039 | No Data | **100** | 500 | 1,000 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 0.019 | 0.0038 | 0.0019 | No Data | **210** | 1,000 | 2,100 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Duster (Dust Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 700 | 3,500 | 7,000 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 0.18 | 0.037 | 0.018 | No Data | **21** | **110** | **210** | No Data |
| | | 0.38 lb ai/dust bag | | 0.093 | 0.019 | 0.0093 | No Data | **42** | **210** | 420 | No Data |
| | | 0.13 lb ai/dust bag | | 0.032 | 0.0064 | 0.0032 | No Data | **120** | 620 | 1,200 | No Data |
| (11b) Dust: Shaker Can | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 0.76 | 0.15 | 0.076 | No Data | **5** | **26** | **52** | No Data |
| | | 0.0038 lb ai/animal | | 0.39 | 0.077 | 0.039 | No Data | **10** | **51** | **100** | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 0.13 | 0.026 | 0.013 | No Data | **30** | **150** | 300 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/ bird | 1,000 birds | 0.15 | 0.030 | 0.015 | No Data | **26** | **130** | **260** | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 0.076 | 0.015 | 0.0076 | No Data | **52** | **260** | 520 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 0.051 | 0.010 | 0.0051 | No Data | **78** | 390 | 780 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/ bird | 1,000 birds | 0.025 | 0.0051 | 0.0025 | No Data | **160** | 780 | 1,600 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 0.074 | 0.015 | 0.0074 | No Data | **54** | **270** | 540 | No Data |
| | | 0.0038 lb ai/animal | | 0.037 | 0.0075 | 0.0037 | No Data | **110** | 530 | 1,100 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 0.013 | 0.0026 | 0.0013 | No Data | 310 | 1,500 | 3,100 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 0.29 | 0.060 | 0.029 | No Data | **13** | **67** | **130** | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 0.15 | 0.029 | 0.015 | No Data | **27** | **130** | **270** | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 0.049 | 0.0098 | 0.0049 | No Data | **80** | 400 | 800 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/ sq ft | 1,000 sq ft | 0.0074 | 0.0015 | 0.00074 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 0.0025 | 0.00049 | 0.00025 | No Data | 1,600 | 8,000 | 16,000 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 0.00065 | 0.00013 | 0.000065 | No Data | 6,100 | 30,000 | 61,000 | No Data |
| | | 0.077 lb ai/gallon | | 0.00063 | 0.00013 | 0.000063 | No Data | 6,300 | 32,000 | 63,000 | No Data |
| | | 0.064 lb ai/gallon | | 0.00052 | 0.00010 | 0.000052 | No Data | 7,600 | 38,000 | 76,000 | No Data |
| | | 0.03 lb ai/gallon | | 0.00024 | 0.000049 | 0.000024 | No Data | 16,000 | 81,000 | 160,000 | No Data |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 0.0013 | 0.00026 | 0.00013 | No Data | 3,000 | 15,000 | 30,000 | No Data |
| | | 0.077 lb ai/gallon | | 0.0013 | 0.00025 | 0.00013 | No Data | 3,200 | 16,000 | 32,000 | No Data |
| | | 0.064 lb ai/gallon | | 0.0010 | 0.00021 | 0.00010 | No Data | 3,800 | 19,000 | 38,000 | No Data |
| | | 0.03 lb ai/gallon | | 0.00049 | 0.000097 | 0.000049 | No Data | 8,100 | 40,000 | 81,000 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 0.00014 | 0.000027 | 0.000014 | No Data | 29,000 | 140,000 | 290,000 | No Data |
| | | 0.00077 lb ai/animal | | 0.000070 | 0.000014 | 0.0000070 | No Data | 57,000 | 280,000 | 570,000 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 0.00040 | 0.000080 | 0.000040 | No Data | 9,900 | 49,000 | 99,000 | No Data |
| | | 0.0017 lb ai/animal | | 0.00031 | 0.000062 | 0.000031 | No Data | 13,000 | 64,000 | 130,000 | No Data |

| Table K.2. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | No Data | No Data | No Data | 570 | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/ sq ft | 100,000 sq ft | 0.035 | No Data | No Data | No Data | **110** | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.014 | No Data | No Data | No Data | **280** | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0070 | No Data | No Data | No Data | 570 | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0016 | No Data | No Data | No Data | 2,400 | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.00081 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.0081 | No Data | No Data | No Data | 490 | No Data | No Data | No Data |

| Table K.2. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.00081 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.0033 | No Data | No Data | No Data | 1,200 | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0016 | No Data | No Data | No Data | 2,400 | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | 0.000812 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| **Mixer/Loader/Applicators** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.018 | 0.0037 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.092 | 0.018 | 0.0092 | No Data | **43** | **220** | 430 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.037 | 0.0073 | 0.0037 | No Data | **110** | 540 | 1,100 | No Data |
| | | 0.00016 lb ai/sq ft | | 0.018 | 0.0037 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | | 0.000080 lb ai/sq ft | | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |

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## Appendix L. Summary of Occupational Handler Cancer Risk Estimates



ED_002155B_00027950-00163

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | 100,000 sq ft | 5E-07 | 9E-08 | 7E-08 | 5E-07 | 9E-08 | 7E-08 | 5E-07 | 9E-08 | 7E-08 | 2E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 4E-07 | 8E-08 | 6E-08 | 4E-07 | 8E-08 | 6E-08 | 4E-07 | 7E-08 | 6E-08 | 2E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 9E-08 | 2E-08 | 1E-08 | 9E-08 | 2E-08 | 1E-08 | 9E-08 | 2E-08 | 1E-08 | 4E-09 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 7E-09 | 6E-09 | 2E-09 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 1E-09 | 2E-10 | 1E-10 | 1E-09 | 2E-10 | 1E-10 | 1E-09 | 2E-10 | 1E-10 | 5E-11 |
| | | 0.064 lb ai/gallon | | 9E-10 | 2E-10 | 1E-10 | 9E-10 | 2E-10 | 1E-10 | 9E-10 | 1E-10 | 1E-10 | 4E-11 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 1E-05 | 2E-06 | 1E-06 | 9E-06 | 6E-07 | 5E-07 | 9E-06 | 5E-07 | 4E-07 | 3E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/ sq ft | | 4E-06 | 6E-07 | 6E-07 | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 2E-07 | 2E-07 | 1E-08 |
| (2b) Mixing/ Loading Wettable Powders for | Poultry (Floor Management – Roost) | 0.080 lb ai/gallon | 2 gallons | 8E-09 | 1E-09 | 1E-09 | 7E-09 | 5E-10 | 4E-10 | 7E-09 | 4E-10 | 3E-10 | 2E-11 |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Paint Applications | | | | | | | | | | | | | |
| (3a) Mixing/ Loading Dusts for Paint Applications (WP Data as Surrogate) | | 0.030 lb ai/gallon | | 8E-09 | 1E-09 | 1E-09 | 7E-09 | 5E-10 | 4E-10 | 7E-09 | 4E-10 | 3E-10 | 2E-11 |
| **Applicators** | | | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 4E-08 | 3E-08 | 1E-08 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 4E-08 | 3E-08 | 1E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 1E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 8E-08 | 2E-08 | 2E-08 | 8E-08 | 2E-08 | 1E-08 | 8E-08 | 2E-08 | 1E-08 | 5E-09 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 3E-08 | 8E-09 | 6E-09 | 3E-08 | 7E-09 | 5E-09 | 3E-08 | 7E-09 | 5E-09 | 2E-09 |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 3E-09 | 3E-09 | 1E-09 |
| | Cattle Feed | 0.0039 | 1,000 | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 3E-09 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (5) Open Pour Liquid Additive for Feed Through Applications | (Concentrate) | lb ai/animal | cows | | | | | | | | | | |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 2E-08 | 3E-09 | 2E-09 | 1E-08 | 3E-09 | 2E-09 | 1E-08 | 3E-09 | 2E-09 | No Data |
| | Horse Feed | 0.0017 lb ai/animal | 500 horses | 6E-09 | 1E-09 | 8E-10 | 6E-09 | 1E-09 | 8E-10 | 6E-09 | 1E-09 | 8E-10 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 4E-09 | 3E-09 | 3E-08 | 4E-09 | 3E-09 | No Data |
| (6a) RTU Pet Collar Applications – 1/99 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 1E-07 | 1E-07 | 4E-06 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 6E-06 | 4E-07 | 4E-07 | 6E-06 | 2E-07 | 2E-07 | 6E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 6E-06 | 4E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 1E-07 | 1E-07 | 4E-06 | 1E-07 | 9E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 8E-06 | 6E-07 | 5E-07 | 8E-06 | 3E-07 | 2E-07 | 8E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 6E-06 | 4E-07 | 4E-07 | 6E-06 | 2E-07 | 2E-07 | 6E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 9E-08 | 3E-06 | 1E-07 | 7E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 6E-07 | 4E-07 | 2E-05 | 5E-07 | 4E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 7E-06 | 5E-07 | 4E-07 | 7E-06 | 3E-07 | 2E-07 | 7E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 1E-07 | 1E-07 | No Data |
| (6b) RTU Pet Collar | Cat (2596-49) | 0.0036 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 1E-07 | 7E-08 | 2E-06 | 9E-08 | 6E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Applications – 50/50 Liquid/Dust Ratio | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 3E-06 | 3E-07 | 2E-07 | 3E-06 | 2E-07 | 1E-07 | 3E-06 | 1E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 2E-06 | 1E-07 | 9E-08 | 2E-06 | 1E-07 | 8E-08 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 1E-07 | 3E-06 | 1E-07 | 9E-08 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 1E-07 | 7E-08 | 2E-06 | 9E-08 | 6E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 4E-06 | 4E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 3E-06 | 3E-07 | 2E-07 | 3E-06 | 2E-07 | 1E-07 | 3E-06 | 1E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 2E-06 | 1E-07 | 1E-07 | 2E-06 | 8E-08 | 6E-08 | 2E-06 | 8E-08 | 5E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 9E-06 | 7E-07 | 6E-07 | 8E-06 | 4E-07 | 3E-07 | 8E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 4E-06 | 3E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 2E-06 | 2E-07 | 2E-07 | 2E-06 | 1E-07 | 8E-08 | 2E-06 | 1E-07 | 7E-08 | No Data |
| (6c) RTU Pet Collar Applications – 99/1 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 1E-07 | 6E-08 | 4E-08 | 1E-07 | 6E-08 | 4E-08 | 1E-07 | 6E-08 | 4E-08 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 2E-07 | 1E-07 | 7E-08 | 2E-07 | 1E-07 | 6E-08 | 2E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 6E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 1E-07 | 7E-08 | 4E-08 | 1E-07 | 7E-08 | 4E-08 | 1E-07 | 7E-08 | 4E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 3E-07 | 1E-07 | 9E-08 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 2E-07 | 1E-07 | 7E-08 | 2E-07 | 1E-07 | 6E-08 | 2E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 1E-07 | 6E-08 | 3E-08 | 1E-07 | 5E-08 | 3E-08 | 1E-07 | 5E-08 | 3E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 4E-07 | 3E-08 | 2E-08 | 4E-07 | 1E-08 | 1E-08 | 4E-07 | 1E-08 | 8E-09 | No Data |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 9E-07 | 3E-08 | 3E-08 | 9E-07 | 3E-08 | 2E-08 | No Data |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 2E-06 | 1E-07 | 9E-08 | 2E-06 | 5E-08 | 4E-08 | 2E-06 | 5E-08 | 3E-08 | No Data |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 9E-08 | 6E-09 | 6E-09 | 9E-08 | 3E-09 | 2E-09 | 9E-08 | 3E-09 | 2E-09 | No Data |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 2E-07 | 2E-08 | 1E-08 | 2E-07 | 8E-09 | 6E-09 | 2E-07 | 7E-09 | 5E-09 | No Data |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 4E-07 | 2E-08 | 2E-08 | 3E-07 | 1E-08 | 9E-09 | 3E-07 | 1E-08 | 8E-09 | No Data |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 6E-07 | 4E-08 | 4E-08 | 6E-07 | 2E-08 | 2E-08 | 6E-07 | 2E-08 | 1E-08 | No Data |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 8E-08 | 6E-08 | 2E-06 | 7E-08 | 5E-08 | No Data |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 9E-08 | 7E-08 | 3E-06 | 8E-08 | 6E-08 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 1E-06 | 8E-08 | 7E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 8E-08 | 3E-06 | 9E-08 | 6E-08 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 1E-07 | 1E-07 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 3E-07 | 2E-08 | 2E-08 | 3E-07 | 1E-08 | 8E-09 | 3E-07 | 9E-09 | 6E-09 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 7E-07 | 5E-08 | 4E-08 | 7E-07 | 2E-08 | 2E-08 | 7E-07 | 2E-08 | 2E-08 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 8E-08 | 7E-08 | 4E-08 | 7E-08 | 7E-08 | 4E-08 | 7E-08 | 7E-08 | 4E-08 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 5E-08 | 1E-07 | 1E-07 | 5E-08 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 2E-08 | 1E-08 | 8E-09 | 1E-08 | 1E-08 | 8E-09 | 1E-08 | 1E-08 | 7E-09 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 2E-08 | 2E-08 | 1E-08 | 2E-08 | 2E-08 | 1E-08 | 2E-08 | 2E-08 | 1E-08 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 5E-08 | 1E-07 | 1E-07 | 5E-08 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 1E-07 | 1E-07 | 7E-08 | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| **Mixers/Loaders/Applicators** | | | | | | | | | | | | | |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | | 0.032 lb ai/animal | | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 7E-07 | 1E-06 | 1E-06 | 6E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 2E-06 | 2E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 9E-07 | 9E-07 | 6E-07 | 8E-07 | 8E-07 | 5E-07 | 8E-07 | 8E-07 | 5E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| | | 0.0013 lb ai/animal | | 5E-08 | 5E-08 | 3E-08 | 4E-08 | 4E-08 | 3E-08 | 4E-08 | 4E-08 | 3E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 7E-07 | 1E-06 | 1E-06 | 6E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 6E-07 | 6E-07 | 4E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-07 | 2E-07 | 2E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 7E-08 | 1E-07 | 1E-07 | 6E-08 | No Data |
| (9b) Liquid: Manually-Pressurized Handwand | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | | 0.032 lb ai/animal | | 4E-05 | 3E-07 | 3E-07 | 4E-05 | 2E-07 | 2E-07 | 4E-05 | 2E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 1E-04 | 7E-07 | 7E-07 | 1E-04 | 5E-07 | 4E-07 | 1E-04 | 5E-07 | 4E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 3E-05 | 2E-07 | 2E-07 | 3E-05 | 2E-07 | 1E-07 | 3E-05 | 1E-07 | 1E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 6E-06 | 4E-08 | 4E-08 | 6E-06 | 3E-08 | 3E-08 | 6E-06 | 3E-08 | 2E-08 | No Data |
| | | 0.0013 lb ai/animal | | 2E-06 | 1E-08 | 1E-08 | 2E-06 | 8E-09 | 7E-09 | 2E-06 | 7E-09 | 6E-09 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 4E-05 | 3E-07 | 3E-07 | 4E-05 | 2E-07 | 2E-07 | 4E-05 | 2E-07 | 2E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 8E-08 | 2E-05 | 9E-08 | 8E-08 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 8E-06 | 6E-08 | 5E-08 | 8E-06 | 4E-08 | 3E-08 | 8E-06 | 4E-08 | 3E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 4E-06 | 3E-08 | 3E-08 | 4E-06 | 2E-08 | 2E-08 | 4E-06 | 2E-08 | 2E-08 | No Data |
| (9c) Liquid: Mechanically -Pressurized Handgun | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 1E-06 | 7E-07 | 6E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 3E-07 | 2E-07 | No Data |
| | | 0.032 lb ai/animal | | 1E-06 | 6E-07 | 5E-07 | 8E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.026 lb ai/animal | | 8E-07 | 5E-07 | 4E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 2E-07 | 1E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 2E-06 | 9E-07 | 7E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 4E-07 | 3E-07 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 2E-07 | 9E-08 | 7E-08 | 1E-07 | 5E-08 | 3E-08 | 1E-07 | 4E-08 | 3E-08 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 4E-08 | 2E-08 | 2E-08 | 3E-08 | 1E-08 | 8E-09 | 3E-08 | 1E-08 | 7E-09 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-06 | 7E-07 | 6E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 3E-07 | 2E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 6E-07 | 5E-07 | 8E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 5E-07 | 3E-07 | 2E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 1E-07 | 9E-08 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-07 | 1E-07 | 9E-08 | 2E-07 | 6E-08 | 4E-08 | 2E-07 | 6E-08 | 4E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-07 | 7E-08 | 6E-08 | 9E-08 | 4E-08 | 3E-08 | 9E-08 | 3E-08 | 2E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-07 | 6E-08 | 5E-08 | 8E-08 | 3E-08 | 2E-08 | 7E-08 | 3E-08 | 2E-08 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 (gallons/ day) | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 3E-09 | 3E-08 | 5E-09 | 3E-09 | No Data |
| | | 0.064 lb ai/gallon | | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 4E-09 | 3E-09 | No Data |
| (10a) Wettable | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Powder: Backpack Sprayer | Swine - Direct Spray | 0.020 lb ai/animal | | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/ sq ft | | 6E-07 | 6E-07 | 4E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | 20,000 sq ft | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 2E-07 | 2E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 3E-09 | 3E-09 | 2E-09 | 3E-09 | 3E-09 | 2E-09 | 3E-09 | 3E-09 | 2E-09 | No Data |
| (10b) Wettable Powder: Manually-Pressurized Handwand | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 1E-07 | No Data |
| | Poultry (Floor Management Litter, | 0.00080 lb ai/sq ft | 20,000 sq ft | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 1E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 8E-08 | 2E-05 | 9E-08 | 8E-08 | No Data |
| | | 0.00016 lb ai/sq ft | | 1E-05 | 7E-08 | 7E-08 | 1E-05 | 5E-08 | 4E-08 | 1E-05 | 5E-08 | 4E-08 | No Data |
| | | 0.000080 lb ai/sq ft | | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 1E-07 | 9E-10 | 8E-10 | 1E-07 | 6E-10 | 5E-10 | 1E-07 | 6E-10 | 5E-10 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 9E-05 | 9E-05 | 9E-05 | 2E-05 | 2E-05 | 2E-05 | 9E-06 | 9E-06 | 9E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 2E-04 | 2E-04 | 2E-04 | 4E-05 | 4E-05 | 4E-05 | 2E-05 | 2E-05 | 2E-05 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 7E-05 | 7E-05 | 7E-05 | 1E-05 | 1E-05 | 1E-05 | 7E-06 | 7E-06 | 7E-06 | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - Plunger Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| (10f) Wettable Powder: Plunger | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 9E-06 | 2E-06 | 2E-06 | 8E-06 | 1E-06 | 1E-06 | 8E-06 | 1E-06 | 1E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 4E-06 | 1E-06 | 9E-07 | 4E-06 | 7E-07 | 6E-07 | 4E-06 | 6E-07 | 5E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Duster (Dust Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 1E-06 | 3E-07 | 3E-07 | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 4E-05 | 1E-05 | 9E-06 | 4E-05 | 7E-06 | 6E-06 | 4E-05 | 6E-06 | 5E-06 | No Data |
| | | 0.38 lb ai/dust bag | | 2E-05 | 5E-06 | 4E-06 | 2E-05 | 3E-06 | 3E-06 | 2E-05 | 3E-06 | 3E-06 | No Data |
| | | 0.13 lb ai/dust bag | | 7E-06 | 2E-06 | 2E-06 | 7E-06 | 1E-06 | 1E-06 | 7E-06 | 1E-06 | 9E-07 | No Data |
| (11b) Dust: Shaker Can | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 4E-04 | 3E-05 | 2E-05 | 4E-04 | 1E-05 | 1E-05 | 4E-04 | 1E-05 | 8E-06 | No Data |
| | | 0.0038 lb ai/animal | | 2E-04 | 1E-05 | 1E-05 | 2E-04 | 7E-06 | 5E-06 | 2E-04 | 6E-06 | 4E-06 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 7E-05 | 5E-06 | 4E-06 | 7E-05 | 2E-06 | 2E-06 | 6E-05 | 2E-06 | 1E-06 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 8E-05 | 5E-06 | 5E-06 | 8E-05 | 3E-06 | 2E-06 | 8E-05 | 2E-06 | 2E-06 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 4E-05 | 3E-06 | 2E-06 | 4E-05 | 1E-06 | 1E-06 | 4E-05 | 1E-06 | 8E-07 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 9E-07 | 7E-07 | 3E-05 | 8E-07 | 6E-07 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 1E-05 | 9E-07 | 8E-07 | 1E-05 | 5E-07 | 3E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | | 0.0038 lb ai/animal | | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 1E-05 | 2E-06 | 1E-06 | 1E-05 | 2E-06 | 1E-06 | 1E-05 | 2E-06 | 1E-06 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 3E-04 | 4E-05 | 4E-05 | 3E-04 | 4E-05 | 3E-05 | 3E-04 | 4E-05 | 3E-05 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | No Data |
| | | 0.077 lb ai/gallon | | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | No Data |
| | | 0.064 lb ai/gallon | | 7E-08 | 1E-08 | 1E-08 | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | No Data |
| | | 0.03 lb ai/gallon | | 3E-07 | 5E-08 | 5E-08 | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 4E-08 | 4E-08 | No Data |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 2E-07 | 9E-08 | 8E-08 | 2E-07 | 6E-08 | 6E-08 | 2E-07 | 6E-08 | 6E-08 | No Data |
| | | 0.077 lb ai/gallon | | 2E-07 | 8E-08 | 8E-08 | 2E-07 | 6E-08 | 6E-08 | 2E-07 | 6E-08 | 5E-08 | No Data |
| | | 0.064 lb ai/gallon | | 2E-08 | 7E-09 | 6E-09 | 2E-08 | 5E-09 | 5E-09 | 2E-08 | 5E-09 | 4E-09 | No Data |
| | | 0.03 lb ai/gallon | | 9E-08 | 3E-08 | 3E-08 | 8E-08 | 2E-08 | 2E-08 | 8E-08 | 2E-08 | 2E-08 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 1E-09 | 7E-10 | 7E-10 | 6E-10 | 2E-10 | 2E-10 | 6E-10 | 1E-10 | 1E-10 | No Data |
| | | 0.00077 lb ai/animal | | 6E-10 | 3E-10 | 3E-10 | 3E-10 | 9E-11 | 9E-11 | 3E-10 | 6E-11 | 6E-11 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 2E-08 | 1E-08 | 1E-08 | 9E-09 | 3E-09 | 3E-09 | 8E-09 | 2E-09 | 2E-09 | No Data |
| | | 0.0017 lb ai/animal | | 1E-08 | 7E-09 | 7E-09 | 7E-09 | 2E-09 | 2E-09 | 7E-09 | 1E-09 | 1E-09 | No Data |

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| Table L.2. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Private/Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 3E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 3E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 | 20,000 birds | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00032 | 20,000 | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.2. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Private/Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | lb ai/sq ft | sq ft | | | | | | | | | | |
| | | 0.00016 lb ai/sq ft | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Mixer/Loader/Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-06 | 7E-07 | 6E-07 | 1E-06 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 2E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 6E-06 | 4E-06 | 3E-06 | 5E-06 | 2E-06 | 1E-06 | 5E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 | 20,000 birds | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 3E-06 | 1E-06 | 1E-06 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 7E-07 | 4E-07 | No Data |
| | | 0.00016 lb ai/sq ft | | 1E-06 | 7E-07 | 6E-07 | 1E-06 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 2E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | 100,000 (sq ft/day) | 2E-06 | 3E-07 | 2E-07 | 2E-06 | 3E-07 | 2E-07 | 2E-06 | 3E-07 | 2E-07 | 7E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | 6E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 5E-08 | 4E-08 | 1E-08 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 1E-07 | 2E-08 | 2E-08 | 1E-07 | 2E-08 | 2E-08 | 1E-07 | 2E-08 | 2E-08 | 6E-09 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 3E-09 | 6E-10 | 4E-10 | 3E-09 | 5E-10 | 4E-10 | 3E-09 | 5E-10 | 4E-10 | 1E-10 |
| | | 0.064 lb ai/gallon | | 3E-09 | 5E-10 | 4E-10 | 3E-09 | 5E-10 | 3E-10 | 3E-09 | 4E-10 | 3E-10 | 1E-10 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 2E-06 | 1E-06 | 9E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 1E-05 | 2E-06 | 2E-06 | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 6E-07 | 5E-07 | 4E-08 |
| (2b) Mixing/ Loading | | 0.080 lb ai/gallon | 2 gallons | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 1E-09 | 1E-09 | 2E-08 | 1E-09 | 1E-09 | 7E-11 |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Wettable Powders for Paint Applications | Poultry (Floor Management – Roost) | | | | | | | | | | | | |
| (3a) Mixing/ Loading Dusts for Paint Applications (WP Data as Surrogate) | | 0.030 lb ai/gallon | | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 1E-09 | 1E-09 | 2E-08 | 1E-09 | 1E-09 | 7E-11 |
| **Applicators** | | | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 1E-07 | 4E-08 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 9E-08 | 6E-07 | 1E-07 | 9E-08 | 4E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 5E-07 | 1E-07 | 1E-07 | 5E-07 | 1E-07 | 8E-08 | 5E-07 | 1E-07 | 8E-08 | 3E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 2E-07 | 6E-08 | 5E-08 | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 5E-08 | 4E-08 | 2E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 1E-07 | 2E-08 | 2E-08 | 9E-08 | 2E-08 | 2E-08 | 9E-08 | 2E-08 | 2E-08 | 7E-09 |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 5E-08 | 1E-08 | 1E-08 | 5E-08 | 1E-08 | 8E-09 | 5E-08 | 1E-08 | 8E-09 | 3E-09 |
| (5) Open Pour Liquid Additive for Feed Through Applications | Cattle Feed (Concentrate) | 0.0039 lb ai/animal | 1,000 cows | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 5E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | No Data |
| | Horse Feed | 0.0017 lb ai/animal | 500 horses | 2E-08 | 3E-09 | 2E-09 | 2E-08 | 3E-09 | 2E-09 | 2E-08 | 3E-09 | 2E-09 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| (6a) RTU Pet Collar Applications – 1/99 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 7E-07 | 5E-07 | 2E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 1E-06 | 8E-07 | 3E-05 | 9E-07 | 7E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 1E-05 | 1E-06 | 9E-07 | 1E-05 | 5E-07 | 4E-07 | 1E-05 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 6E-07 | 4E-07 | 2E-05 | 5E-07 | 4E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 2E-05 | 2E-06 | 1E-06 | 2E-05 | 9E-07 | 6E-07 | 2E-05 | 8E-07 | 5E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 7E-07 | 5E-07 | 2E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 1E-06 | 8E-07 | 3E-05 | 9E-07 | 7E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 9E-06 | 3E-07 | 3E-07 | 9E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 5E-05 | 3E-06 | 3E-06 | 5E-05 | 2E-06 | 1E-06 | 5E-05 | 2E-06 | 1E-06 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 2E-05 | 2E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 1E-05 | 1E-06 | 8E-07 | 1E-05 | 5E-07 | 4E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| (6b) RTU Pet Collar Applications - 50/50 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 6E-06 | 5E-07 | 4E-07 | 6E-06 | 3E-07 | 2E-07 | 6E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 9E-06 | 5E-07 | 3E-07 | 9E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 8E-06 | 6E-07 | 5E-07 | 7E-06 | 4E-07 | 3E-07 | 7E-06 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 9E-06 | 7E-07 | 6E-07 | 9E-06 | 4E-07 | 3E-07 | 8E-06 | 4E-07 | 3E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 6E-06 | 5E-07 | 4E-07 | 6E-06 | 3E-07 | 2E-07 | 6E-06 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 1E-05 | 1E-06 | 9E-07 | 1E-05 | 6E-07 | 4E-07 | 1E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 9E-06 | 5E-07 | 3E-07 | 9E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 2E-05 | 1E-06 | 9E-07 | 2E-05 | 1E-06 | 8E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 1E-05 | 1E-06 | 8E-07 | 1E-05 | 6E-07 | 4E-07 | 1E-05 | 5E-07 | 4E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 7E-06 | 6E-07 | 5E-07 | 7E-06 | 4E-07 | 3E-07 | 7E-06 | 3E-07 | 2E-07 | No Data |
| (6c) RTU Pet Collar Applications - 99/1 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 5E-07 | 2E-07 | 2E-07 | 5E-07 | 2E-07 | 2E-07 | 5E-07 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 8E-07 | 5E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 8E-07 | 4E-07 | 2E-07 | 8E-07 | 4E-07 | 2E-07 | 8E-07 | 4E-07 | 2E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| Mixers/Loaders/Applicators | | | | | | | | | | | | | |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | | 0.032 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | | 0.0013 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 4E-07 | 4E-07 | 3E-07 | 4E-07 | 4E-07 | 2E-07 | 4E-07 | 4E-07 | 2E-07 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | No Data |
| (9b) Liquid: | | 0.039 | 400 | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Manually-Pressurized Handwand | Beef Cattle - Direct Applied | lb ai/animal | animals | | | | | | | | | | |
| | | 0.032 lb ai/animal | | 1E-04 | 9E-07 | 8E-07 | 1E-04 | 6E-07 | 5E-07 | 1E-04 | 5E-07 | 5E-07 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 3E-04 | 2E-06 | 2E-06 | 3E-04 | 1E-06 | 1E-06 | 3E-04 | 1E-06 | 1E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 1E-04 | 7E-07 | 7E-07 | 1E-04 | 5E-07 | 4E-07 | 1E-04 | 4E-07 | 4E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 2E-04 | 1E-06 | 1E-06 | 2E-04 | 9E-07 | 8E-07 | 2E-04 | 8E-07 | 7E-07 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 9E-08 | 8E-08 | 2E-05 | 8E-08 | 7E-08 | No Data |
| | | 0.0013 lb ai/animal | | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-04 | 9E-07 | 8E-07 | 1E-04 | 6E-07 | 5E-07 | 1E-04 | 5E-07 | 5E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 9E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-05 | 1E-07 | 1E-07 | 1E-05 | 7E-08 | 6E-08 | 1E-05 | 7E-08 | 6E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-05 | 9E-08 | 8E-08 | 1E-05 | 6E-08 | 5E-08 | 1E-05 | 5E-08 | 5E-08 | No Data |
| (9c) Liquid: | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Mechanically -Pressurized Handgun | | 0.032 lb ai/animal | | 3E-06 | 2E-06 | 1E-06 | 2E-06 | 9E-07 | 6E-07 | 2E-06 | 9E-07 | 5E-07 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.026 lb ai/animal | | 3E-06 | 1E-06 | 1E-06 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 7E-07 | 4E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 5E-06 | 3E-06 | 2E-06 | 4E-06 | 1E-06 | 1E-06 | 3E-06 | 1E-06 | 8E-07 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 5E-07 | 3E-07 | 2E-07 | 4E-07 | 1E-07 | 1E-07 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 1E-07 | 7E-08 | 6E-08 | 9E-08 | 4E-08 | 3E-08 | 9E-08 | 3E-08 | 2E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 6E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3E-06 | 2E-06 | 1E-06 | 2E-06 | 9E-07 | 6E-07 | 2E-06 | 9E-07 | 5E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-06 | 9E-07 | 7E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 4E-07 | 3E-07 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 4E-07 | 2E-07 | 2E-07 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 6E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 3E-07 | 2E-07 | 1E-07 | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 5E-08 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 gallons | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| | | 0.064 lb ai/gallon | | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| (10a) Wettable Powder: Backpack Sprayer | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | | 8E-07 | 8E-07 | 6E-07 | 8E-07 | 8E-07 | 5E-07 | 8E-07 | 7E-07 | 5E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 4E-07 | 4E-07 | 3E-07 | 4E-07 | 4E-07 | 2E-07 | 4E-07 | 4E-07 | 2E-07 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 1E-08 | 1E-08 | 7E-09 | 9E-09 | 9E-09 | 6E-09 | 9E-09 | 9E-09 | 6E-09 | No Data |
| (10b) Wettable | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Powder: Manually-Pressurized Handwand | Swine - Direct Spray | 0.020 lb ai/animal | | 7E-05 | 5E-07 | 5E-07 | 7E-05 | 4E-07 | 3E-07 | 7E-05 | 3E-07 | 3E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 7E-05 | 5E-07 | 5E-07 | 7E-05 | 4E-07 | 3E-07 | 7E-05 | 3E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | | 0.00016 lb ai/sq ft | | 3E-05 | 2E-07 | 2E-07 | 3E-05 | 1E-07 | 1E-07 | 3E-05 | 1E-07 | 1E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 1E-05 | 1E-07 | 1E-07 | 1E-05 | 7E-08 | 6E-08 | 1E-05 | 7E-08 | 6E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 4E-07 | 3E-09 | 3E-09 | 4E-07 | 2E-09 | 2E-09 | 4E-07 | 2E-09 | 1E-09 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 3E-04 | 3E-04 | 3E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 7E-04 | 7E-04 | 7E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 2E-04 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Plunger Data as Surrogate) | | | | | | | | | | | | | |
| (10f) Wettable Powder: Plunger Duster (Dust Data as Surrogate) | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 3E-05 | 6E-06 | 6E-06 | 3E-05 | 4E-06 | 4E-06 | 2E-05 | 4E-06 | 3E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 1E-05 | 3E-06 | 3E-06 | 1E-05 | 2E-06 | 2E-06 | 1E-05 | 2E-06 | 2E-06 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 4E-06 | 9E-07 | 8E-07 | 4E-06 | 6E-07 | 5E-07 | 4E-06 | 6E-07 | 5E-07 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 1E-04 | 3E-05 | 3E-05 | 1E-04 | 2E-05 | 2E-05 | 1E-04 | 2E-05 | 2E-05 | No Data |
| | | 0.38 lb ai/dust bag | | 6E-05 | 1E-05 | 1E-05 | 6E-05 | 1E-05 | 9E-06 | 6E-05 | 9E-06 | 8E-06 | No Data |
| | | 0.13 lb ai/dust bag | | 2E-05 | 5E-06 | 5E-06 | 2E-05 | 3E-06 | 3E-06 | 2E-05 | 3E-06 | 3E-06 | No Data |
| (11b) Dust: Shaker Can (Plunger Data Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 1E-03 | 8E-05 | 7E-05 | 1E-03 | 4E-05 | 3E-05 | 1E-03 | 4E-05 | 3E-05 | No Data |
| | | 0.0038 lb ai/animal | | 6E-04 | 4E-05 | 4E-05 | 6E-04 | 2E-05 | 2E-05 | 6E-04 | 2E-05 | 1E-05 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 2E-04 | 1E-05 | 1E-05 | 2E-04 | 7E-06 | 5E-06 | 2E-04 | 6E-06 | 4E-06 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/ bird | 1,000 birds | 2E-04 | 2E-05 | 1E-05 | 2E-04 | 8E-06 | 6E-06 | 2E-04 | 7E-06 | 5E-06 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 1E-04 | 8E-06 | 7E-06 | 1E-04 | 4E-06 | 3E-06 | 1E-04 | 4E-06 | 3E-06 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 8E-05 | 5E-06 | 5E-06 | 8E-05 | 3E-06 | 2E-06 | 8E-05 | 2E-06 | 2E-06 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 4E-05 | 3E-06 | 2E-06 | 4E-05 | 1E-06 | 1E-06 | 4E-05 | 1E-06 | 8E-07 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | | 0.0038 lb ai/animal | | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 5E-06 | 4E-06 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 8E-04 | 1E-04 | 1E-04 | 8E-04 | 1E-04 | 1E-04 | 8E-04 | 1E-04 | 1E-04 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 3E-06 | 4E-07 | 4E-07 | 3E-06 | 4E-07 | 3E-07 | 3E-06 | 4E-07 | 3E-07 | No Data |
| | | 0.077 lb ai/gallon | | 3E-06 | 4E-07 | 4E-07 | 3E-06 | 4E-07 | 3E-07 | 3E-06 | 3E-07 | 3E-07 | No Data |
| | | 0.064 lb ai/gallon | | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | No Data |
| | | 0.03 lb ai/gallon | | 1E-06 | 1E-07 | 1E-07 | 1E-06 | 1E-07 | 1E-07 | 1E-06 | 1E-07 | 1E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 7E-07 | 3E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | No Data |
| | | 0.077 lb ai/gallon | | 7E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | No Data |
| | | 0.064 lb ai/gallon | | 6E-08 | 2E-08 | 2E-08 | 5E-08 | 2E-08 | 1E-08 | 5E-08 | 1E-08 | 1E-08 | No Data |
| | | 0.03 lb ai/gallon | | 3E-07 | 1E-07 | 9E-08 | 2E-07 | 7E-08 | 7E-08 | 2E-07 | 7E-08 | 6E-08 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 3E-09 | 2E-09 | 2E-09 | 2E-09 | 5E-10 | 5E-10 | 2E-09 | 3E-10 | 3E-10 | No Data |
| | | 0.00077 lb ai/animal | | 2E-09 | 1E-09 | 1E-09 | 1E-09 | 3E-10 | 3E-10 | 9E-10 | 2E-10 | 2E-10 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 5E-08 | 3E-08 | 3E-08 | 3E-08 | 8E-09 | 8E-09 | 3E-08 | 5E-09 | 5E-09 | No Data |
| | | 0.0017 lb ai/animal | | 4E-08 | 2E-08 | 2E-08 | 2E-08 | 6E-09 | 6E-09 | 2E-08 | 4E-09 | 4E-09 | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (10c) Wettable Powder: | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 5E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 7E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 3E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loader/Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 7E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 2E-05 | 1E-05 | 9E-06 | 1E-05 | 6E-06 | 4E-06 | 1E-05 | 5E-06 | 3E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 8E-06 | 4E-06 | 4E-06 | 6E-06 | 2E-06 | 2E-06 | 6E-06 | 2E-06 | 1E-06 | No Data |
| | | 0.00016 lb ai/sq ft | | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 7E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/22/2017 8:37:42 PM
**To**: Nguyen, Khue [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53463f4f956d4772a6ada2f68debfcb8-Nguyen, Khue]
**Subject**: RE: can you send me the entire team list for TCVP?
**Attachments**: Cholecalciferol.docx; Tetrachlorvinophos.doc; Zinc Phosphide Overview May 2015.docx

Hi Khue,

The team is listed below. I also attached the summary sheets for my cases which were assigned to you above.

**HED** –Linda Taylor (Tox), Danette Drew (Chem. + RA) and Wade Britton/Kelly Lowe (ORE), Branch Chief: Mike Metzger **EFED ERB4 Charles Peck** and Mary Clock-Rust Branch Chief: Jean Holmes and RAPL is Katrina White **BEAD** – Tim Kiely (BC) Andrew Lee, Don Atwood and Jihad Alsadek **RD** – Richard Gebkin (PM) and Carmen Rodia

James Parker, M.S.
Chemical Review Manager
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**From:** Nguyen, Khue
**Sent:** Wednesday, February 22, 2017 1:51 PM
**To:** Parker, James <Parker.James@epa.gov>
**Subject:** can you send me the entire team list for TCVP?

...I cannot find it among all the documents you sent.

Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division
Office of Pesticide Programs, EPA

703-347-0248
Nguyen.khue@epa.gov

Appointment

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/16/2017 5:15:09 PM
**To**: Nguyen, Khue [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53463f4f956d4772a6ada2f68debfcb8-Nguyen, Khue]; Biggio, Patricia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2a9a640a9a2941c5a9be1c4967e71718-Biggio, Pat]
**BCC**: DCRoomPYS9671/Potomac-Yard-One [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=user18c48aa6]

**Subject**: Tetrachlorvinphos HED Revised Risk Assessment Discussion
**Attachments**: TCVP revised human health assessment dec2016.pdf; TCVP PID Mitigation Proposal 1.10.17.docx; TCVP RA one-pager 1.31.17..docx
**Location**: DCRoomPYS9671/Potomac-Yard-One

**Start**: 2/16/2017 9:00:00 PM
**End**: 2/16/2017 9:30:00 PM
**Show Time As**: Tentative

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM**

**Date:** December 21, 2016

**SUBJECT:** **Tetrachlorvinphos (TCVP)** Revised Human Health Risk Assessment for Registration Review

**PC Code:** 083701, 083702
**Petition No.:** NA
**Risk Assessment Type:** Single Chemical Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** 436834
**Registration Nos.:** NA
**Regulatory Action:** Registration Review
**Case No.:** 1321
**CAS No.:** 22248-79-9
**40 CFR:** §180.252

**FROM:** Danette Drew, Chemist
Linda Taylor, Ph.D. Toxicologist
Kelly Lowe, Environmental Scientist
Risk Assessment Branch V/VII
Health Effects Division (HED, 7509P)

And

Wade Britton, MPH, Environmental Health Scientist
Risk Assessment Branch IV
Health Effects Division (HED, 7509P)

**THROUGH:** Michael Metzger, Branch Chief
Risk Assessment Branch V/VII
Health Effects Division (HED, 7509P)

**TO:** James Parker, Chemical Review Manager
Neil Anderson, Branch Chief
Risk Management and Implementation Branch I
Pesticide Re-evaluation Division (7508P)

Attached is HED's revised human health risk assessment in support of the registration review of the insecticide tetrachlorvinphos (TCVP).



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## 1.0 Executive Summary

The insecticide tetrachlorvinphos (TCVP) [(Z)-2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate] is a member of the organophosphate (OP) class of pesticides. TCVP is used as a dermal or oral treatment to livestock (i.e., cattle, swine, poultry and horses) and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs. Formulations for pet use include collars, dusts/powders, and pump and trigger sprays. The other (non-pet) uses include dusts (D), emulsifiable concentrates (EC), feed through (solid and liquid food additives), feed blocks, and wettable powders (WP). Human exposure to TCVP in food may occur as a result of consuming residues in animal commodities (e.g., meat). Exposure may also occur from drinking water that may contain TCVP residues as a result of some outdoor use patterns. Residential exposures may occur as a result of applying flea products to pets (cats and dogs) or contacting treated pets. Occupational exposures may occur during application of TCVP to livestock or their premises, or during outdoor perimeter or kennel treatments. Occupational exposures may also occur to veterinarians and pet groomers. Exposure via spray drift is not anticipated based on the current use patterns.

The most recent human health risk assessment for TCVP was completed in December 2015 (D. Drew *et al.*, 12/21/2015, *Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment (DRA) for Registration Review*, D411095). The current TCVP risk assessment reflects the following changes since the 2015 risk assessment:

- The reduction of the oral toxicological point of departure (POD) from 8.0 mg/kg/day to 2.8 mg/kg/day based on additional red blood cell (RBC) acetylcholinesterase (AChE) inhibition data identified during this re-evaluation in the current acute comparative cholinesterase assay (CCA) study in rats.

- The use of the literature study, Davis, M. et al., *Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos.* Journal of Exposure Science and Environmental Epidemiology ((2008) 18, 564-57), (*hereinafter* Davis study), following approval for its use in risk assessment by the Human Studies Review Board (HSRB) in January 2016. Previously, risk estimates from both a surrogate residue transfer study (i.e., an amitraz pet collar study[1]) and the Davis literature study were presented. HED is now relying solely on the Davis study data since these chemical-specific data have been approved by the HSRB for use and result in a higher estimated exposure potential (i.e., are more health protective) than the surrogate data.

- Following a reassessment of the mutagenicity data available on TCVP, the relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be

[1] MRID 49468801: *Determination of Transferable Residues of Amitraz from the Hair of Dogs Following the Application of the Preventic® Collar.*

established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[2].

- Following the Dec. 21, 2015 TCVP risk assessment, information was submitted during the public comment period to address whether the active ingredients in TCVP pet collars are released as a liquid or solid (dust) form, or both. The submitted information describes that both a liquid and particulate, or dust, are present on the surface of the pet collar. Therefore, HED has assumed that TCVP could be transferred in either form from the collar to the pet's fur and result in the potential for post-application exposures from contact with the treated pet. HED has assessed exposures resulting from the TCVP pet collar uses assuming that the TCVP pet collar product exists as a liquid and solid form concurrently at varying ratios (e.g., 1/99, 50/50, and 99/1 liquid/dust). [See Section 6.0 of this document for a complete description of this approach].

This document also addresses, where appropriate, the comments received during the public comment period following publication of the 2015 TCVP draft human health risk assessment. A comprehensive response to comments received is also provided in the following memo: D. Drew et al., *Tetrachlorvinphos (TCVP) Health Effects Division Response to Comments on the December 21, 2015 Draft Human Health Risk Assessment for TCVP Registration Review*, D433403, 12/21/2016).

*Hazard*

TCVP is a member of the OP class of pesticides. For TCVP, like other OPs, the initiating event in the adverse outcome pathway/mode of action (AOP/MOA) involves inhibition of the enzyme acetylcholinesterase (AChE) *via* phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For TCVP, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. TCVP does not require metabolic activation to an oxon to inhibit AChE; i.e., the parent compound is the active form inhibiting AChE. OPs generally exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same dose, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks; a pattern that is observed for most OPs, but not every OP, like TCVP, which shows no difference in response across duration. For TCVP the steady state is

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[2] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.



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reached after a single day of exposure. As such, the endpoint selection for TCVP considers data available for all durations of dosing when choosing the most protective point of departure.

The toxicology database for TCVP is complete except the requirement for additional mutagenicity studies [a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and an assay that examines possible genotoxic activity in the target (liver) organ] (McCarroll, 2016; TXR No. 0057226)[3]. TCVP has cholinesterase data across multiple lifestages, durations, and routes for both red blood cell (RBC) and brain cholinesterase inhibition. There are acceptable studies available for toxicity endpoint and point of departure (POD) selection. For TCVP, RBC AChE inhibition is the most sensitive endpoint and is the endpoint from which the PODs for all TCVP exposure routes and durations were selected.

There is no evidence of quantitative or qualitative sensitivity in the developmental rat and rabbit studies or in the gestational (fetus) or juvenile components of the comparative cholinesterase assay (CCA) studies in rats. AChE data from the CCA studies suggest that the fetus is not more sensitive than the pregnant dam, and that pregnant females are not more sensitive than non-pregnant females with respect to cholinesterase inhibition. When comparing RBC $BMD_{10}$ (benchmark dose) estimates from across the acute (single dose) CCA and repeat dose CCA studies, it is apparent that there are no age-related (or duration-related) differences. The acute and steady state PODs selected for oral exposure risk assessment are based on RBC AChE inhibition in the postnatal day 11 (PND11) and postnatal day 21 (PND21) pups in the acute CCA since they provide the most robust dose-responses and are protective of all life stages. Although the steady state dietary POD was selected from an acute CCA, the acute study is considered appropriate for longer term durations since AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose.

High quality AChE data for the dermal and inhalation routes are also available and allow for route specific evaluation. RBC AChE inhibition was observed in both sexes in the inhalation study (brain AChE was not assessed), while no inhibition of RBC or brain AChE was observed in the dermal study up to the limit dose. A non-cancer dermal assessment is not required for TCVP; however, a cancer dermal assessment is required. The dermal absorption factor is 9.6% for TCVP.

TCVP is classified as a Group C possible human carcinogen (based on statistically significant increases in combined hepatocellular adenoma/carcinoma in female mice) with a linear low-dose approach for quantification of risk using the oral slope factor (Q1*) of $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$. Whereas parent compound TCVP is the residue of concern for AChE inhibition, TCVP plus metabolites containing the 2,4,5 trichlorobenzene moiety are the residues of concern for cancer assessment. Following a reassessment of the mutagenicity data available on TCVP, it was determined that the relevance of the mutagenic findings to the tumorigenic response seen in

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[3] *Ibid.*



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female mice cannot be established. Following the submission and review of the required mutagenicity assays, the need for an updated cancer assessment will be determined.

For TCVP, as for other OPs, the FQPA safety factor (SF) of 10X has been retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

For the acute and steady state dietary assessments, a total uncertainty factor of 1000X is appropriate for infants, children, youths and females of childbearing age (10X to account for interspecies extrapolation and 10X for intraspecies variation and the 10X FQPA SF). The only population subgroup for dietary exposure scenarios for which the FQPA SF is not retained is adults 50-99 years of age; therefore, the total uncertainty factor for that population is 100X.

A total uncertainty factor of 1000X is appropriate for residential incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF). A total uncertainty factor of 300X is appropriate for all inhalation exposures: 3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments (or a 10X database uncertainty factor for occupational assessments to protect potentially pregnant female workers) due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

*Tolerances*

Tolerances for residues of TCVP are established under 40 CFR §180.252 for livestock commodities based on oral feed-through and direct dermal uses on livestock (cattle, swine, and poultry). The residues of concern for tolerance enforcement are tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol (frequently abbreviated as TCVP, TCVPdeme, TCPEol , TCPEone, and TCPEdiol, respectively). The current tolerance expression under 40 CFR §180.252 includes all of these residues except des-O-methyl tetrachlorvinphos; this metabolite should be included in the tolerance expression. The current tolerance levels should be updated in the 40 CFR as discussed in Section 2.2.3.
There are no Codex maximum residue limits (MRLs) established or proposed for residues of TCVP. Canada has established MRLs for plant (apple and grape) and livestock commodities. The differences in U.S. and Canadian residue definitions prohibit harmonization.

*Dietary Risk Assessment*

Acute (TCVP), steady state (TCVP), and cancer (TCVP plus metabolites containing the 2,4,5 trichlorobenzene moiety) dietary (food and drinking water) exposure and risk assessments were conducted using the DEEM-FCID v3.16 model. The dietary exposure analyses for TCVP are mostly refined. The only food forms included in the analyses are based on animal commodities. The food residues were based upon U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) monitoring data except where no appropriate PDP data were available (i.e.,



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residues from poultry dermal application studies were used for poultry fat and skin). The Biological and Economic Analysis Division (BEAD) of OPP provided percent of livestock treated information. Model-derived estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effect Division (EFED). A distribution of EDWCs was used probabilistically in the acute and steady state analyses. For the cancer analysis, the EDWC was included as a single point estimate.

The acute dietary (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 190% of the aPAD. When drinking water is analyzed by itself, the acute dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95$^{th}$ and 99.9$^{th}$ percentile of exposure.

The steady state (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the steady state population adjusted dose (ssPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 120% of the ssPAD. The steady state dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95$^{th}$ and 99.9$^{th}$ percentile of exposure.

*Residential Handler Risk Assessment*

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are assumed to complete all elements of an application without use of any protective equipment.

Residential TCVP handler exposures are anticipated to be short- (1 to 30 days) and intermediate-term (1 to 6 months) in duration. However, because of the steady state AChE inhibition exhibited by the OPs (typically 21 days and longer for OPs, but 1 day to reach steady state for TCVP), steady state exposures were assessed and presented for residential exposures to TCVP pet products. Residential handler exposures to TCVP pet products may occur via the dermal or inhalation routes while the product is placed on a cat or dog. Both steady state non-cancer and cancer residential handler exposure assessments were performed for adult homeowners applying TCVP pet collars, dusts/powders, and pump/trigger sprays products to cats and dogs. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are assessed.

<u>Residential Handler Steady State (Non-Cancer):</u>

Pet Collars: Because there is uncertainty as to whether the TCVP pet collars are liquid and/or dust formulated products, residential handler (adult) steady state inhalation exposures were evaluated assuming both liquid and dust residues are present simultaneously at varying ratios



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(e.g., 1/99, 50/50, and 99/1 liquid/dust). Unit exposure (UE) data (for handler exposure), and residue transfer data and transfer coefficients (for post-application exposure) specific to each formulation type were used. For handlers, the liquid formulation assessment used spot-on surrogate UE data, which assumes negligible inhalation exposure; therefore, only the dust-specific UE data (i.e., a TCVP dust/powder applicator exposure study) is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure. No non-cancer inhalation risks of concern were identified for residential handlers for any liquid/dust formulation ratio assumption (all MOEs ≥ level of concern (LOC) of 300). When assuming a ratio of 1/99 liquid/dust, MOEs range from 920 to 4,600; when assuming a ratio of 50/50 liquid/dust, MOEs range from 1,800 to 9,100; and when assuming a ratio of 99/1 liquid/dust, MOEs range from 91,000 to 450,000.

Dust/Powder and Pump/Trigger Spray: All residential handler (adult) non-cancer steady state inhalation risks estimated for the TCVP pet dust/powder and pump/trigger spray formulations are not of concern (i.e., all MOEs are > 300; LOC = 300; range = 3,200 to 160,000).

Residential Handler Cancer:

Pet Collars: Residential handler cancer risks (combined dermal and inhalation) estimated for TCVP pet collars assuming 1/99 and 50/50 liquid/dust formulation ratios are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$.

Dust/Powder and Pump/Trigger Spray: Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$.

*Residential Post-Application Risk Assessment*

There is the potential for post-application exposure for individuals exposed as a result of contacting a cat or dog previously treated with TCVP pet products (dusts/powders, pump/trigger sprays, pet collars). Since there is no non-cancer dermal hazard for TCVP, a quantitative non-cancer post-application dermal exposure assessment was not performed for adults or children. A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from applications to pets. The quantitative exposure/risk assessment for residential post-application exposures is based on incidental oral (hand-to-mouth) exposure to children (1 to < 2 years old) from contacting cats and dogs treated with TCVP. While not the only lifestage potentially exposed for these post-application scenarios, this lifestage is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential TCVP post-application exposures are anticipated to be short- (1 to 30 days), intermediate-term (1 to 6 months), and long-term (>6 months – *for pet collar scenarios only*) in duration. However, because of the steady state AChE inhibition exhibited by the OPs, steady state exposures were assessed and presented for residential exposures to TCVP pet products.

Residential Post-Application Steady State (Non-Cancer):

Pet Collars: As was done for residential handlers, due to the uncertainty as to whether the TCVP pet collars are liquid and/or dust formulated products, residential post-application exposures were evaluated assuming both liquid and dust residues are present simultaneously at varying ratios (e.g., 1/99, 50/50, and 99/1 liquid/dust). For post-application exposure from pet collars, the same data were used to estimate transferable residues for both liquid and dust formulations; however, the transfer coefficients used to assess potential post-application exposure to dust formulations are much higher compared to those used for liquid formulations. Therefore, as with handlers, the post-application risk estimates are driven by the presence of dust in the formulations. Children's incidental oral (hand-to-mouth) steady state exposures to pets treated with TCVP collars are estimated to be of concern regardless of the ratio of liquid/dust assumed (i.e., MOEs < 1000; LOC = 1000). When assuming a 1/99 liquid/dust formulation ratio, MOEs range from 0.91 to 7.4. When assuming a 50/50 liquid/dust formulation, MOEs range from 1.8 to 15, and when assuming a 99/1 liquid/dust formulation, MOEs range from 65 to 530.

Dust/Powder and Pump/Trigger Spray: Children's incidental oral (hand-to-mouth) steady state exposures to pets treated with TCVP dust/powders are estimated to be of concern (MOEs range from 98 to 640; LOC = 1000). However, children incidental oral exposures to pets treated with TCVP pump/trigger spray products are estimated not to be of concern (i.e., MOEs are > 1000; MOEs range from 1,600 to 15,000).

Residential Post-Application (Cancer):

Pet Collars: Residential post-application cancer (adult; dermal only as post-application inhalation exposure is negligible for this use) risk estimates for TCVP pet collars assuming 1/99 or 50/50 liquid/dust formulation ratios range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1 liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$.

Dust/Powder and Pump/Trigger Spray: Residential post-application cancer (adult; combined dermal and inhalation) risks estimated for TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$.

*Spray Drift*

A quantitative spray drift assessment was not conducted because the use of TCVP for direct animal treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs are either 1) not applied via aircraft, groundboom, or airblast equipment or 2) for applications to poultry buildings with groundboom equipment, the use is indoors and not anticipated to be a significant source of spray drift.

*Aggregate Risk Assessment*

The acute aggregate risk assessment combines exposures to TCVP from food and drinking water. There are acute risk estimates of concern for food only; therefore, a quantitative acute aggregate

risk assessment was not conducted. The steady state aggregate assessment includes the steady state dietary (food and drinking water) and residential exposures. However, because there are risks of concern associated with both dietary (food) and residential exposure, a quantitative steady state aggregate risk assessment was not conducted. If mitigation occurs such that the risks for the individual contributors to the aggregate risk are acceptable, a quantitative assessment may be completed at that time.

The cancer aggregate risk assessment combines residential and dietary (food and drinking water) expected lifetime exposures for adults. For TCVP, a cancer aggregate assessment was performed for adult handlers and for adult post-application activities related to residential pet product use.

The residential handler cancer aggregate assessment uses exposures from applying TCVP products to pets. The cancer aggregate assessment combines the highest (worst case, upper bound) handler exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type. The cancer aggregate (dietary and residential exposures) risk estimates for handlers for the upper bound exposures for collars, dust/powders, and pump/trigger sprays are in the $10^{-7}$ to $10^{-6}$ range

The residential post-application cancer aggregate assessment uses exposures from contacting pets treated with TCVP products. The cancer aggregate assessment combines the highest (worst case, upper bound) post-application exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type. The cancer aggregate (dietary and residential exposures) post-application risk estimates for the upper bound exposures for collars, dust/powders, and pump/trigger sprays range from $10^{-6}$ to $10^{-4}$.

*Occupational Handler Risk Assessment*

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. Occupational handler exposures to TCVP may occur via the dermal or inhalation routes while the mixing/loading and applying products registered for dermal or oral treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs (professional pet handlers).

Occupational handler exposure is expected to be short- and intermediate-term in duration. However, because of the steady state AChE inhibition exhibited by the OPs, steady state exposures were assessed and presented for occupational exposures to TCVP products. Both steady state non-cancer and cancer handler exposure assessments were performed. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment

includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are assessed.

Occupational Handler Steady State (Non-Cancer):

Of the 198 total occupational handler exposure scenarios assessed, the majority (162) are not of concern (i.e., steady state inhalation MOEs are $\geq 300$; LOC = 300) with currently required personal protective equipment (PPE) (i.e., respiratory protection). Of the remaining 36 handler exposure scenarios, an additional 25 are not of concern with consideration of increasing levels of respiratory protection (i.e., 11 occupational handler exposure scenarios result in estimated risks of concern despite the addition of respiratory protection or engineering controls).

Occupational Handler Cancer:

Occupational cancer risks were estimated for both private/farmer and contract/commercial handlers. Cancer risk estimates, with currently required PPE, range from $10^{-10}$ to $10^{-5}$ for private/farmer handlers and from $10^{-10}$ to $10^{-4}$ for contract/commercial handlers.

*Occupational Post-Application Risk Assessment*

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties.

Occupational post-application exposures are not anticipated for TCVP as the majority of application scenarios are not to foliar surfaces. The use of TCVP outdoors as a perimeter treatment is not expected to result in occupational post-application exposure as reentry activities related to crop production (e.g., scouting, harvesting) are not anticipated for this use pattern.

*Human Studies Review*

This risk assessment relies in part on data from studies in which human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from Pesticide Handler Exposure Database (PHED) 1.1; the AHETF database; the Residential SOPs (Treated Pets); as well as a TCVP dust/powder applicator exposure study (MRID 45519601), a mixer/loader/applicator wettable powder study (MRID 42622301), and TCVP dust and pump spray study (MRID 45485501): (1) are subject to ethics review pursuant to 40 CFR Part 26, (2) have received the review necessary for consideration in this risk assessment, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have

included review by the HSRB. Descriptions of data sources, as well as guidance on their use, can be found at the agency website.[4]

Data were also used from a literature study using TCVP pet collars, Davis, M. *et. al., Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos.* Journal of Exposure Science and Environmental Epidemiology. (2008) 18, 564-57). On January 12-13, 2016 the EPA HSRB met to address the scientific and ethical charge questions related to the Davis study. The HSRB concluded that, "the research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol used in the study can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars."[5]

*CropLife America Petition*

On November 29, 2016, CropLife America (CLA) submitted a petition to EPA asking the agency to "halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner." Any interim or final registration review decision for TCVP could potentially be impacted by EPA consideration of the epidemiological studies identified in the CLA petition. EPA is therefore placing a copy of the CLA petition in the registration review docket for TCVP. In the near future, EPA intends to publish a notice on its Pesticide Website announcing the receipt of the CLA petition and opening a comment period on the petition. Persons wishing to comment on the petition should respond to EPA in connection with that comment period.

## 2.0 HED Recommendations

### 2.1 Data Deficiencies

A follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and a study that investigates possible genotoxic activity in the target organ (liver) are required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target).

Based on the findings from the mutagenicity revisit, HED is recommending that TCVP be assayed in a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395)

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[4] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

[5] Letter from Liza Dawson, PhD, Chair of the EPA HSRB to Thomas Burke, PhD, MPH, EPA Science Advisor. Subject: January 12-13, 2016 EPA Human Studies Review Board Meeting Report. March 30, 2016.

using both sexes, an appropriate sample size (5/sex/dose/sacrifice time) and oral treatment (dietary would be the best fit for the risk assessment). HED further recommends that the assay should cover the range of doses used in the 1980 Hazleton study (MRID 00117443) that will span the tumorigenic dose range for both sexes and the conditions should simulate conditions in the Amer et al., 1983 study. An additional study which would investigate possible genotoxic activity in the target organ (*i.e.,* mouse liver) should be performed. This assay with the target tissue would be appropriate and should follow a similar protocol as described above and should examine DNA damage potential (*e.g.,* Comet assay, DNA adduct formation or any other DNA target)[6].

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

A gas liquid chromatography (GLC) method for the determination of TCVP *per se* in livestock commodities is described in the Pesticide Analytical Method (PAM), Vol. II, as Method I.

The registrant has submitted a method (14020.6106) for the determination of tetrachlorvinphos and its metabolites (TCVPdeme, TCPEdiol, TCPEone and TCPEol) in livestock commodities, which uses QuEChERS and LC/MS/MS methods. The test data for method 14020.6106 are classified as scientifically acceptable for use as an analytical method for ruminant and poultry commodities.

The submitted multiresidue method testing data are acceptable and indicate that FDA multiresidue methods are not suitable for analysis of the TCVP metabolites TCPEdiol and TCVPdeme. However, the metabolites TCPEol and TCPEone were recoverable under Protocol F, although fortified recoveries were small (<50%).

It should be noted that the FDA PESTDATA database dated 8/93 (PAM Vol. I, Appendix II) indicates that parent compound TCVP is completely recovered (>80%) using FDA multiresidue method protocol D (section 232.4) but is not recovered using protocol E (Sections 211.1/231.1 and 212.1/232.1, fatty and nonfatty matrices).

### 2.2.2 International Harmonization

There are no Codex maximum residue limits (MRLs) established or proposed for residues of TCVP. Canada has established MRLs for plant (apple and grape) and livestock commodities. The U.S. tolerances are for livestock commodities; there are no registered crop uses. Canada's residue definition is 2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate (TCVP) and its

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[6] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

low melting isomer as opposed to the U.S. definition which includes the parent compound TCVP plus the four metabolites of concern. The differences in U.S. and Canadian residue definitions prohibit harmonization. HED has not examined the Canadian registrations; different use patterns may also be a factor in achieving harmonization. A summary of U.S. and international tolerances and maximum residue limits is presented in Appendix F.

### 2.2.3 Recommended Tolerances

Tolerances for residues of TCVP in livestock commodities are established under 40 CFR §180.252. The current tolerance expression is for the combined residues of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] and its metabolites, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol.

The HED Metabolism Committee has determined that the residues of concern for tolerance enforcement are tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. The current tolerance expression under 40 CFR §180.252 includes all of these residues *except des-O-methyl tetrachlorvinphos*; this metabolite should be included in the tolerance expression. To allow separate risk assessments for 1) cholinesterase inhibition (parent TCVP only) and 2) carcinogenicity (parent plus metabolites), the tolerances for each livestock commodity should also specify the maximum residues of TCVP *per se* from the total residues. The tolerance definition should be modified as follows, to be consistent with the Tolerance Expression Guidance issued 5/27/09 (S. Knizner).

Tolerances are established for residues of the insecticide tetrachlorvinphos, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate) and its metabolites chloro- 1 -(2,4,5-trichlorophenyl)-vinylmonomethyl phosphate, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol, calculated as the stoichiometric equivalent of tetrachlorvinphos, in or on the commodity.

**Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos.**

| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
|---|---|---|---|---|
| Cattle, fat (of which no more than 0.1 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat | 1.0 | *Cattle, fat (of which no more than 0.6 ppm is tetrachlorvinphos per se)* |

| Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos. | | | | |
|---|---|---|---|---|
| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
| Cattle, kidney (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 1.0 | -- | Remove | See cattle, meat byproducts |
| Cattle, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.5 | -- | Remove | |
| Cattle, meat (of which no more than 2.0 ppm is tetrachlorvinphos *per se*) | 2.0 | 0.27 (0.21) muscle | 0.3 | *Cattle, meat (of which no more than 0.2 ppm is tetrachlorvinphos per se)* |
| Cattle, meat by products, except kidney and liver | 1.0 | -- | Remove | See cattle, meat byproducts |
| Cattle, meat by products | None | 0.16 (<0.01) liver; 0.28 (0.015) kidney; 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat; 0.27 (0.21) muscle | 1.0 | *Cattle, meat byproducts (of which no more than 0.6 ppm is tetrachlorvinphos per se)* [5] |
| Egg (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.288 (0.026) | 0.3 | *Egg (of which no more than 0.03 ppm is tetrachlorvinphos per se)* |
| Hog, fat (of which no more than 0.1 ppm is tetrachlorvinphos *per se*) | 0.2 | 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat | 1.0 | *Hog, fat (of which no more than 0.6 ppm is tetrachlorvinphos per se)* |
| Hog, kidney (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 1.0 | -- | Remove | See hog, meat byproducts |
| Hog, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.5 | -- | Remove | |
| Hog, meat (of which no more than 2.0 ppm is tetrachlorvinphos *per se*) | 2.0 | 0.27 (0.21) muscle | 0.3 | *Hog, meat (of which no more than 0.2 ppm is tetrachlorvinphos per se)* |
| Hog, meat byproducts, except kidney and liver | 1.0 | -- | Remove | See hog, meat byproducts |
| Hog, meat by products | None | 0.16 (<0.01) liver; 0.28 (0.015) kidney; 0.84 (0.56) subcutaneous fat; 0.75 (0.34) peritoneal fat; 0.27 (0.21) muscle | 1.0 | *Hog, meat byproducts (of which no more than 0.6 ppm is tetrachlorvinphos per se)* [5] |

| Table 2.2.3. Tolerance Reassessment Summary for Tetrachlorvinphos. | | | | |
|---|---|---|---|---|
| Commodity | Established Tolerance [1] (ppm) | Maximum Residues [2] (ppm) | Reassessed Tolerance [3,4] (ppm) | Comments; *Correct Commodity Definition* |
| Milk, fat (reflecting negligible residues in whole milk and of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.05 | 0.072 (0.036) for milk; 0.078 (<0.01) for cream | 0.1 | *Milk (of which no more than 0.04 ppm is tetrachlorvinphos per se)* |
| Poultry, fat (of which no more than 7.0 ppm is tetrachlorvinphos *per se*) | 7.0 | 1.298 (0.099) abdominal fat | 1.4 | *Poultry, fat (of which no more than 0.1 ppm is tetrachlorvinphos per se)* |
| Poultry, liver (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | 2.0 | | Remove | See poultry, meat byproducts |
| Poultry, meat (of which no more than 3.0 ppm is tetrachlorvinphos *per se*) | 3.0 | 0.40 (0.082) muscle | 0.4 | *Poultry, meat (of which no more than 0.1 ppm is tetrachlorvinphos per se)* |
| Poultry, meat byproducts, except liver | 2.0 | -- | Remove | See poultry, meat byproducts |
| Poultry, meat byproducts | None | 0.52 (0.016) liver; 0.58 (0.022) kidney; 0.40 (0.082) muscle; 19.41 (6.03) skin with fat; 1.30 (0.099) abdominal fat | 20 | *Poultry, meat byproducts (of which no more than 6.0 ppm is tetrachlorvinphos per se)* [5] |

[1] Time-limited tolerances; current tolerance expression is for the combined residues of tetrachlorvinphos [(Z)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate] and its metabolites, 1-(2,4,5-trichlorophenyl)-ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)-ethanediol; expression should also include des-O-methyl tetrachlorvinphos.

[2] Total residues of tetrachlorvinphos and its metabolites, TCVP-deme, TCPEone, TCPEol (free and conjugated forms), and TCPEdiol (free and conjugated), expressed in terms of parent equivalents; the value in parentheses represents the maximum residues of the parent tetrachlorvinphos.

[3] Reassessed tolerance is based on the maximum residue from the respective magnitude of the residue study; the maximum residues of the parent tetrachlorvinphos are reported in the corrected commodity definition.

[4] The residue data for cattle can be used to set tolerances for hog commodities since residues in hog tissues are not likely to be greater than those in cattle tissues.

[5] According to the 18 July 2007 Minutes of the HED ChemSAC meeting, the guidance document will be revised to include language detailing the use of the highest residue data for any tissue (liver, kidney, fat, skin or muscle) to determine the tolerance for meat byproducts. A single tolerance on "meat byproducts" will be recommended based on that highest residue, and individual tolerances will no longer be set on liver, kidney, or meat byproducts (except liver and kidney).

## 2.3 Label Recommendations

### 2.3.1 Recommendations from Residue Reviews

The following label revisions are recommended based on the application methods and rates used in the tetrachlorvinphos magnitude of the residue studies, which were used to determine the appropriate tolerance levels in livestock commodities (GLN 860.1200 Directions for Use):

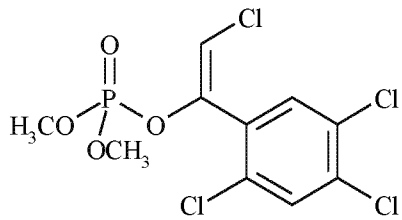
- Based on the magnitude of the residue study on cattle, the product labels with direct animal spray uses on cattle (EPA Reg. Nos. 61483-43 and 61483-50) should be amended to specify a maximum of three applications, with two-week retreatment intervals, at 19 g ai/animal/dose. The product label for Ravap (EPA Reg. No. 61483-50) should also be amended to provide conversion factors to allow calculation of direct animal spray treatment rate in terms of g ai/animal.

- Based on the magnitude of the residue study on poultry, the product labels with direct animal spray uses on poultry (EPA Reg. Nos. 61483-43 and 61483-50) should be amended to specify a maximum of seven applications (with two-week retreatment intervals) at 0.18 g ai/hen/application. Note that the label should specify the weight or volume of the product to be applied.

## 3.0 Introduction

### 3.1 Chemical Identity

**Table 3.1. Tetrachlorvinphos Nomenclature.**

| | |
|---|---|
| Compound |  |
| Common name | Tetrachlorvinphos |
| Company experimental name | TCVP |
| IUPAC name | (Z)-2-chloro-1-(2,4,5-trichlorophenyl) vinyl dimethyl phosphate |
| CAS registry number | 22248-79-9 |

See Appendices D and E for nomenclature and physical/chemical properties of TCVP and metabolites (TCVPdeme, TCPEdiol, TCPEone and TCPEol, TCCEol, TCBA).

### 3.2 Physical/Chemical Characteristics

Technical tetrachlorvinphos is a tan to brown crystalline solid with a melting point of 93-98 °C. TCVP is not expected to volatilize significantly due to a low vapor pressure of $2.6 \times 10^{-7}$ torr (25°C). The solubility of tetrachlorvinphos in water at 25°C is 11.6 mg/L. TCVP has limited solubility in most aromatic hydrocarbons. TCVP is hydrophobic, with an octanol-water partition coefficient of 3350 (Log $K_{ow}$ of 3.53).



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### 3.3 Pesticide Use Pattern

TCVP is used as a direct animal treatment to livestock (i.e., cattle, horses, poultry and swine) and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs. The TCVP livestock and perimeter treatment uses are formulated as follows: dusts (D), emulsifiable concentrates (EC), feed through (solid, granular and pelleted/tableted) and liquid food additives), feed blocks, and wettable powders (WP). TCVP can be applied by a variety of means/equipment types including: backrubber/facerubber; backpack; cup; groundboom; handheld fogger; manually-pressurized handwand; mechanically-pressurized handwand; open pour (dust and liquid formulations); paint (airless sprayer or brush/roller); pet collar; plunger; rotary duster; shaker can; spoon; stationary fogger; and trigger spray. For a complete list of registered uses, including maximum use rates, see Appendix A of D436833 (W. Britton, 12/2016, *Tetrachlorvinphos: Final Occupational and Residential Exposure Assessment for Registration Review*).

### 3.4 Anticipated Exposure Pathways

Humans may be exposed to TCVP residues in food since TCVP may be directly applied to, or fed to, livestock which may result in residues in animal commodities. TCVP may reach surface and ground water sources of drinking water through the outdoor usage on poultry droppings, garbage and manure piles, and kennels and corrals. Residential exposures (handler and post-application) may occur as a result of the application to dogs and cats as dust/powders, sprays, or collars. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational post-application exposures are not expected as reentry activities are not anticipated for the registered TCVP uses.

### 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.epa.gov/compliance/environmentaljustice/resources/policy/exec_order_12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks

for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

## 4.0 Hazard Characterization and Dose-Response Assessment

TCVP is a member of the organophosphate class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway/mode of action (AOP/MOA) for TCVP involves inhibition of the enzyme AChE *via* phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). TCVP is in the oxon form and does not require bioactivation prior to inhibiting AChE. For TCVP, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating this toxicology database.

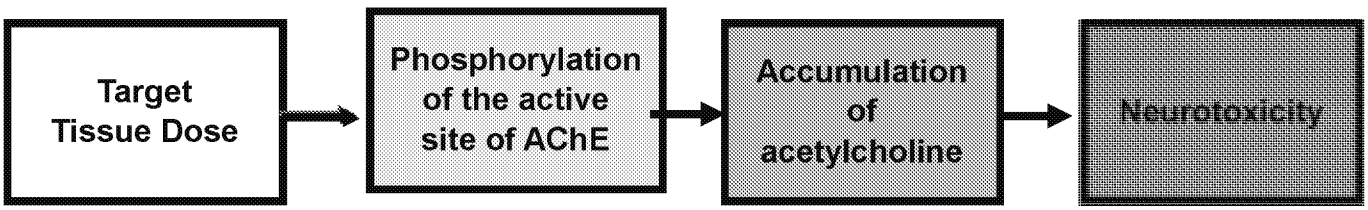


**Figure 1. Adverse outcome pathway for OPs**

### 4.1 Toxicology Studies Available for Analysis

The toxicology database for TCVP is complete except for a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and an *in vivo* assay to examine DNA damage potential (*e.g.,* Comet assay, DNA adduct formation, or any other DNA target)[7].

There are acceptable studies available for toxicity endpoint selection; they include:

- subchronic oral toxicity studies in rats
- chronic oral toxicity studies in rats and dogs
- carcinogenicity studies in rats and mice
- developmental studies in rats and rabbits
- reproduction study in rats

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[7] *Ibid.*

- acute and subchronic neurotoxicity studies in rats
- developmental neurotoxicity (DNT) study in rats
- acute and repeated comparative (CCA) cholinesterase (ChE) studies in juvenile and adult rats
- repeated, gestational ChE study in pregnant rats and fetuses
- delayed neurotoxicity study in hens
- subchronic dermal toxicity study in rats
- repeated dosing inhalation toxicity study in rats
- immunotoxicity study in mice
- complete mutagenicity study battery
- dermal penetration study in rats
- metabolism study in rats

## 4.2 Absorption, Distribution, Metabolism, & Excretion (ADME)

TCVP, unlike some other OPs, does not require metabolic activation to the oxon form to inhibit AChE. In a rat metabolism study, TCVP was almost completely metabolized, and most of the radiolabel was excreted in the urine (46%-60%) and feces (38%-56%) within 48 hours of dosing. Only minor amounts (>0.5%) were found in the tissues. Very little un-metabolized parent compound was recovered. The major metabolite in feces was trichlorophenylethanol, with lesser amounts of trichlorophenylethandiol. The major metabolite in urine was trichloromandelic acid, with lesser amounts of desmethyl tetrachlorvinphos. There is no evidence of bioaccumulation. Some differences in metabolism were noted between the sexes; *e.g.,* males excreted more trichloromandelic acid, a more completely metabolized form of TCVP, whereas females excreted more of the desmethyl TCVP, which could be derived from TCVP with only a single metabolic step.

### 4.2.1 Dermal Absorption

There is a dermal absorption study in rats, which provides a dermal absorption factor (DAF) of 9.6%. In an acceptable *in vivo* dermal penetration study in rats (MRID 42111501), male rats were treated at 0.01, 0.1, 1, and 5 mg/cm$^2$ and sacrificed at 0.5, 1, 2, 4, or 10 hours post dose. Based on total amount of radioactivity recovered from urine, tissues, feces, and carcass after 10 hours of dermal exposure, 84% of the applied dose (0.1 mg/cm$^2$) was recovered in the wash and 9.57% was in the skin, urine, feces, and carcass. The DAF was used to evaluate dermal exposures in the cancer risk assessment. However, since there was no dermal hazard identified for non-cancer endpoints in the dermal toxicity study on TCVP; *i.e.,* no AChE inhibition at the limit dose and no concern for increased susceptibility after repeat exposure, a quantitative dermal assessment was not performed (see Section 4.6.1).

## 4.3 Toxicological Effects



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AChE inhibition is the well-established cholinergic mode of action for OPs and is typically used as the critical effect in hazard characterization for members of this class of pesticides. TCVP inhibits AChE in various species including rats, mice, rabbits, and dogs and is the most sensitive effect in the database. TCVP has AChE data across multiple lifestages (fetal, post-natal, adult), durations (single to 104 weeks), and routes (oral, dermal, inhalation) for both red blood cell (RBC) and brain AChE inhibition. However, when looking at the AChE inhibition data across the numerous studies and datasets, it is apparent that there is no consistent pattern as to the relative sensitivity of the RBC and brain compartments, sex, or life stage. For instance, at a single dose of 10 mg/kg, male RBC and brain AChE were similarly inhibited in both adults (-17% and -13% respectively) and PND11 pups (-14% and -14%, respectively). Additionally, as is observed for some OPs, the oral AChE data demonstrate no increase in inhibition with repeated exposures as compared to a single dose. Specifically, the acute single dose CCA data show $BMD_{10}$ of 6.5, with the 11-day repeated exposure $BMD_{10}$ of 7.7 in adult male rats (see Section 4.3.2).

Transient clinical signs [gait alterations, constricted pupils, tremors (fore- and hindlimb), body cool to the touch, decreased defecation, red material on forelimbs, around eyes, nose, mouth] characteristic of cholinergic toxicity were observed in the acute neurotoxicity rat study, and tremors were observed in pregnant rats in the developmental toxicity study at dose levels 100X higher and 5X higher than those eliciting AChE inhibition, respectively. The hen study was negative for indications of delayed neurotoxicity.

There is no evidence of quantitative or qualitative sensitivity in the developmental rat and rabbit studies or in the rat reproduction study following pre-natal and/or postnatal exposure to TCVP. In the rat developmental toxicity study, no developmental effects were observed in the fetus. Developmental toxicity (increased early resorptions, post-implantation loss, and decreased number of live fetuses) was observed in the rabbit developmental toxicity study at the same dose level where significant toxicity (mortality, abortion) was observed in the maternal rabbit. No reproductive or offspring toxicity was observed in the 2-generation reproductive rat study, but increased adrenal weights were observed in the parental rats.

AChE data from the CCA study suggest that the fetus is not more sensitive than the pregnant dam, and that pregnant females are not more sensitive than non-pregnant females with respect to cholinesterase inhibition. When comparing RBC $BMD_{10}$ estimates from across the repeat (48773401) and acute studies (48773401a), it is apparent that there are no age-related (or duration-related) differences. For instance, the $BMD_{10}$ estimates range from 3.2 mg/kg in PND21 male rats to 5.0 mg/kg in PND11 male rats and to 6.5 mg/kg in adult males in the acute CCA study and from 8.6 mg/kg/day in adult female to 20.5 mg/kg/day in the PND 11 pups in the repeat CCA study. Furthermore, the points of departure (POD) used for risk assessment, which are based on cholinesterase inhibition in the PND11 and PND21 animals, since they provide the most robust BMD and BMDL dose-responses, are protective of all life stages.

In the developmental neurotoxicity study (DNT), quantitative susceptibility was observed in pups (decreased pup weight, decreased relative brain weight/measurements) but only at the high

dose of 200 mg/kg/day where maternal toxicity was not demonstrated. However, a 200 mg/kg/day dose to adult female rats in the repeat dose CCA study resulted in 62% RBC and 57% brain cholinesterase inhibition, indicating significant toxicity occurred in the dam in the DNT at this dose. The 200 mg/kg/day dose to the juvenile rats is 20-fold higher than doses reflecting approximately 10%-20% inhibition in juvenile pups in the CCA study and 70-fold higher than the point of departure. Therefore, when considered in combination with the results from the CCA, the high dose of the DNT is not of concern for risk assessment. The BMDs relied upon from the CCA study are protective of the effects observed in pups at higher doses in the DNT study.

TCVP is classified as a Group C possible human carcinogen with a linear low-dose approach for quantification of risk using the oral slope factor (Q1*) of $1.83 \times 10^{-3}$.

In acute lethality studies, TCVP has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is a slight dermal irritant, a moderate eye irritant, and a dermal sensitizer.

### 4.3.2 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined and focused on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute, single dosing, and repeated dosing studies in laboratory animals for TCVP. This analysis provides the basis for determining which exposure durations are appropriate for assessing the human health risk. Table 4.3.2.1 provides a summary of the representative results from experimental toxicology studies with TCVP.

**Table 4.3.2.1 – TCVP $BMD_{10}$ Results (mg/kg/day) for RBC and Brain AChE Inhibition Over Time in Adult Rats**

| MRID (study) | Days of Dosing | % inhibition at LOAEL (mg/kg) or the $BMD_{10}$ [1] | |
|---|---|---|---|
| | | **RBC** | |
| | | **Males** | **Females** |
| MRID 48773401a | 1 day | 10% at 6.5 ($BMD_{10}$) | 10% at 14.9 ($BMD_{10}$) |
| MRID 48773401 (repeat CCA) | 11 days | 10% at 7.7 ($BMD_{10}$) | 10% at 8.7 ($BMD_{10}$) |
| MRID 45570601 (21-day oral) | 21 days | No inhibition | 10% at 9.9 ($BMD_{10}$) |
| MRID 43371201 (90-day oral) | 90 days | 10% at 61.6 ($BMD_{10}$) | 10% at 10.5 ($BMD_{10}$) |
| MRID 42980901 (chronic oral) | 365 days | No inhibition | 29% at 63 |
| | | **Brain** | |

| Table 4.3.2.1 – TCVP $BMD_{10}$ Results (mg/kg/day) for RBC and Brain AChE Inhibition Over Time in Adult Rats | | | |
|---|---|---|---|
| **MRID (study)** | **Days of Dosing** | **% inhibition at LOAEL (mg/kg) or the $BMD_{10}$ [1]** | |
| | | **Males** | **Females** |
| MRID 48773401a | 1 day | 10% at 7.4 ($BMD_{10}$) | 10% at 11.6 ($BMD_{10}$) |
| MRID 48294601 (acute CCA) | 1 day | 10% at 6.8 ($BMD_{10}$) | 10% at 11.3 ($BMD_{10}$) |
| MRID 48773401 (repeat CCA) | 11 days | 10% at 33.8 ($BMD_{10}$) | 10% at 7.2 ($BMD_{10}$) |
| MRID 45570601 (21-day oral) | 21 days | No inhibition | 10% at 14.7 ($BMD_{10}$) |
| MRID 43371201 (90-day oral) | 90 days | No inhibition | 12% at 6.7 |
| MRID 42980901 (chronic oral) | 365 days | No inhibition | 14% at 63 |

[1]The BMD, not the BMDL, estimates are shown when available in Table 4.3.2.1. According to the BMD guidance, the central estimate (i.e., the BMD) is used for purposes of comparison. The LOAEL and percent inhibition is presented when a BMD estimate is not available.

In adults, OPs generally exhibit a phenomenon known as steady state cholinesterase (AChE) inhibition. After repeated dosing at the same dose, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks; a pattern that is observed for most OPs, but not every OP, like TCVP, which shows no difference in response across duration. For TCVP, the results in Table 4.3.2.1 show a similar response across durations suggesting that steady state is reached after a single day of exposure. Further, TCVP exhibits a shallow dose-response curve for cholinesterase inhibition; *i.e.*, large increases in administered dose result in only small changes in AChE inhibition, although this may be attributed to differences in time after dosing that the cholinesterase measurements were made. This shallow dose response leads to variability in the AChE data and a relatively broad range of values of3.2 to 61.6 mg/kg/day for $BMD_{10}$s and 2.8 to 26.3 mg/kg/day for $BMDL_{10}$s (Appendix B). Given the results in Table 4.3.2.1 for TCVP, single day and steady state durations should have the same point of departure for human health risk assessment. As such, the endpoint selection for TCVP considers data available for all durations of dosing when choosing a protective POD.

## 4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for TCVP. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised

draft human health risk assessment ((D424485, D. Drew et al., 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al., 12/29/2014). Initially, the agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[8]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years. For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al., 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al., 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate (DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP)

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[8] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.-1; CDC, 2008)[9]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

**Table 4.4.1. CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).**

| Pesticide | DMP | DMTP | DMDTP | DEP | DETP | DEDTP |
|---|---|---|---|---|---|---|
| Azinphos methyl | X | X | X | | | |
| Chlorethoxyphos | | | | X | X | |
| Chlorpyrifos | | | | X | X | |
| Chlorpyrifos methyl | X | X | | | | |
| Coumaphos | | | | X | X | |
| Dichlorvos (DDVP) | X | | | | | |
| Diazinon | | | | X | X | |
| Dicrotophos | X | | | | | |
| Dimethoate | X | X | X | | | |
| Disulfoton | | | | X | X | X |
| Ethion | | | | X | X | X |
| Fenitrothion | X | X | | | | |
| Fenthion | X | X | | | | |
| Isazaphos-methyl | X | X | | | | |
| Malathion | X | X | X | | | |
| Methidathion | X | X | X | | | |
| Methyl parathion | X | X | | | | |
| Naled | X | | | | | |
| Oxydemeton-methyl | X | X | | | | |
| Parathion | | | | X | X | |
| Phorate | | | | X | X | X |
| Phosmet | X | X | X | | | |
| Pirimiphos-methyl | X | X | | | | |
| Sulfotepp | | | | X | X | |
| Temephos | X | X | | | | |
| Terbufos | | | | X | X | X |
| Tetrachlorvinphos | X | | | | | |
| Trichlorfon | X | | | | | |

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

[9] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf



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For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al., 2014; Eskenazi et al., 2007; Whyatt et al., 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al., 2010; Whyatt et al., 2004; Rauh et al., 2011). The CHARGE study (Shelton et al., 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al., 2008; Chen et al., 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al., 2008; Chen et al., 2012; Racke et al., 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al., 2008; Forsberg et al., 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al. (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and Attention Deficit Hyperactivity Disorder (ADHD) were reported by three prospective cohorts [Rauh et al., 2006; Eskenazi et al., 2007; Marks et al., 2010; and Fortenberry et al. (2014)] with additional support from a cross-sectional study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al. (2014) found suggestive evidence of an association with TCPy and ADHD in boys, whereas statistically significant associations were observed by Rauh et al. (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al. (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al. (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In

contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al. (2010), which may in part account for the difference in the observed results from these studies.

In addition, the three US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al., 2007; Furlong et al., 2014). Specifically, Furlong et al. (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al. (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al. (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al. (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al. (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al. ,2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK-PD) model (D424485, D. Drew et al., 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[10] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al., 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al., 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated with the lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al., 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children

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[10] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increase in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the TCVP human health risk assessment, a value of 10X has been applied. Similarly, a database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

### 4.5 Safety Factor for Infants and Children (FQPA Safety Factor)

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety Factor will be retained for TCVP for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.** [11]

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[11] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

### 4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for TCVP is complete and includes developmental toxicity studies in the rat and rabbit, a reproductive toxicity study in the rat, acute and subchronic neurotoxicity studies in the rat, a developmental neurotoxicity study in the rat, a three component comparative cholinesterase study in the rat (acute, repeat, and gestational exposure), and an acute delayed hen neurotoxicity study.

As discussed in Section 4.5, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

### 4.5.2 Evidence of Neurotoxicity

TCVP is an organophosphate insecticide with an established neurotoxic AOP; neurotoxicity is the most sensitive effect in all species, routes, and lifestages and is being used to derive points of departure (PODs). Neurotoxicity related to inhibition of AChE by TCVP, which was noted in the ACN and rabbit developmental toxicity studies, included transient clinical signs characteristic of cholinergic toxicity and tremors, as discussed above. The points of departure selected for this risk assessment are protective of these clinical signs.

### 4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The concern for susceptibility is low based on the lack of susceptibility following *in utero* exposure to TCVP in either the rat or rabbit developmental toxicity study or following *in utero* and/or pre-/post-natal exposure to TCVP in the 2-generation reproduction rat study. The apparent quantitative susceptibility observed in pups in the DNT occurred at the same dose level where 60% RBC and 45% brain cholinesterase inhibition occurred in pups and 62% RBC and 57% brain inhibition occurred in the adult females in the repeat CCA study. This comparison demonstrates that significant inhibition and toxicity also occurred in the maternal rat in the DNT, and repeat dosing showed no sensitivity with respect to the magnitude of the cholinesterase inhibition between the dam and pups. Furthermore, the effects observed in the DNT occurred at a dose 70-fold higher than the point of departure (POD). The POD is based on the AChE data from PND11 and PND21 pups from the acute CCA study, which provided the lowest POD, and is protective of the effects observed in the DNT.

As discussed in Section 4.5, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

### 4.5.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The mostly refined dietary risk assessment uses food residues levels from monitoring data and from empirical studies, percent livestock treated data and model-estimated drinking water concentrations from maximum application rates. Residential exposure assessments use data from surrogate and chemical-specific sources. The exposure assumptions will not underestimate risks.

## 4.6 Toxicology Endpoint and Point of Departure Selections

### 4.6.1 Dose-Response Assessment

Table 4.6.4.1 summarizes the TCVP toxicity endpoints and points of departure (PODs) selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: For TCVP, there is no consistent pattern across studies, durations, lifestages, and routes. Following acute oral exposure, RBC and brain are equally affected, whereas the RBC compartment provided the lower BMDL estimate following repeat oral exposure in adults. Also, for each age group in the CCA studies, the magnitude of the RBC and brain inhibition is similar. Based upon the robustness of the AChE data and dose-response across the dose selection in the acute dose CCA rat study (see Appendix B for BMD analysis results), the RBC AChE data from PND 11 and 21 male and female pups were selected as the endpoint for deriving the acute and steady state POD for risk assessment.
- *Potentially susceptible populations (fetuses, juveniles, pregnant dams)*: The available AChE data across multiple lifestages (adults, pregnant females, fetuses, juveniles) show no quantitative sensitivity following repeat or acute exposure. The fetus is not more sensitive than the pregnant dam, and pregnant females were not more sensitive than non-pregnant females. There is also no consistent pattern with respect to sex difference. In the acute CCA, the adult male shows greater inhibition in both compartments than the adult female, whereas the adult female shows more inhibition (both compartments) in the repeat CCA and other repeat dose studies than the adult male.
- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with the exposure scenario(s) of interest. In the case of TCVP, there are single and repeat dose oral, repeat dose dermal, and repeat dose inhalation studies that contain measurements of RBC and brain AChE inhibition.
- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with the exposure duration of interest. In the case of TCVP, there are single day and steady state/repeat exposure oral studies and steady state dermal and inhalation studies. The oral AChE data show the magnitude of AChE inhibition does not significantly increase with time such that AChE inhibition from a single oral exposure is comparable to AChE inhibition after repeated oral exposure.
- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across



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studies. Based on a weight of evidence approach, the TCVP database allows for PODs to be derived from the most conservative BMDLs, which are consistent for the PND 11 and PND 21 rats in the acute CCA and adult animals in the acute and repeat CCA thereby increasing the confidence in such values.

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated $BMD_{10}$s and $BMDL_{10}$s. The $BMD_{10}$ is the estimated dose where AChE is inhibited by 10% compared to background AChE activity. The $BMDL_{10}$ is the lower confidence bound on the $BMD_{10}$ value. As a matter of science policy, the agency uses the BMDL, not the BMD, as the PoD (USEPA, 2012). All BMD/BMDL modeling was completed using USEPA BMD Software, version 2.4; an exponential model was used to fit the data. Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix A of this document, which includes an additional acute CCA identified since the last risk assessment. Summary tables of BMD analyses can be found in Appendix B and the technical details of the analysis can be found in the BMD memo (J. Bever; TXR No. 0056970; D420286).

*Acute Dietary (All Populations)*

A POD for the acute dietary (all populations) exposure scenario was derived from the results of the high quality, well-conducted acute dose CCA study (MRID 448773401a) in juvenile rats. Numerous estimates informed the $BMDL_{10}$ of 2.8 mg/kg/day, which was associated with RBC AChE inhibition in PND11 and PND 21 male and female juvenile rats and was therefore selected as the POD for the acute dietary exposure scenario for all populations. The lowest corresponding $BMD_{10}$ was 3.2 mg/kg/day. Data from the young rat from the acute CCA study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations.

The FQPA SF (10X) will be retained for infants, children, youths, and women of childbearing age due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5). The acute population adjusted dose (aPAD) for these lifestages is 0.0028 mg/kg/day (includes a total uncertainty factor of 1000X: 10X to account for interspecies extrapolation and 10X for intraspecies variation and the 10X FQPA SF). The only population subgroup for dietary exposure scenarios for which the FQPA SF is not retained is adults 50-99 years of age; therefore, the aPAD for this population subgroup is 0.028 mg/kg/day.

*Steady-State Dietary (All Populations)*

A POD for the steady-state dietary (all populations) exposure scenarios was derived from the same acute dose CCA study used for the acute dietary. A $BMDL_{10}$ of 2.8 mg/kg/day associated with RBC cholinesterase inhibition in male and female PND 11 and 21 rats was selected as a suitable POD for the steady-state dietary exposure scenario. The lowest corresponding $BMD_{10}$ was 3.2 mg/kg/day. Although the steady state dietary endpoint was selected from an acute dose comparative cholinesterase study, the duration of this study is considered appropriate for this exposure scenario since AChE data across the TCVP database demonstrate that there is no

progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose. A longer-term exposure does not result in a lower POD, as evidenced by the larger $BMD_{10}$s found for the repeat dose CCA data.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) is applied to the $BMDL_{10}$ to obtain an ssPAD of 0.0028 mg/kg/day for exposure scenarios with infants, children, youth, and women of child-bearing age. The only population subgroup for which the FQPA SF is not retained is adults 50-99; therefore, the ssPAD for this population subgroup is 0.028 mg/kg/day.

*Incidental Oral, Steady State*

For the purpose of assessing potential risk associated with incidental oral exposure from steady state durations, OPP selected the same POD (2.8 mg/kg/day) and endpoint as selected above for dietary exposure.

A total uncertainty factor of 1000X is appropriate for incidental oral exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)). The Level of Concern (LOC) for incidental oral exposures is 1000.

*Dermal, Steady State*

No quantification of dermal non-cancer risk is required for TCVP since there were: (1) no treatment related effects (no clinical signs) at doses up to and including the limit dose of 1000 mg/kg/day in the dermal toxicity study; (2) both RBC and brain cholinesterase activity were assessed in the dermal study and neither compartment was affected at the limit dose; (3) there is no concern for quantitative susceptibility for juvenile or gestational lifestages based on results of the developmental, reproductive, or CCA toxicity studies.

*Inhalation, Steady State*

The steady state inhalation POD was selected from a 4-week inhalation toxicity study (MRID 48803501) in rats, based on an increase in RBC cholinesterase inhibition in both sexes. Females had slightly higher modeled values ($BMDL_{10}$ of 0.022 mg/L/day: $BMD_{10}$ of 0.12 mg/L/day) than males. The duration of this study is considered appropriate for the steady state exposure scenario since steady state occurs within 21 days, as demonstrated for other OPs, and a longer-term exposure would not be expected to result in a lower POD. The methods and dosimetry equations described in the agency's reference concentration (RfC) guidance are suited for calculating human equivalent concentrations (HECs) based on the inhalation toxicity POD obtained in rats exposed for 6 hours/day for an average of 5.5 days/week. The regional deposited dose ratio (RDDR), which accounts for the particulate diameter (mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD] of aerosols) can be used to estimate the different dose fractions deposited along the respiratory tract surface areas. Thus, the RDDR can

be used to adjust an observed inhalation particulate exposure of an animal to the predicted inhalation exposure for a human. For the subchronic inhalation toxicity study with TCVP, an RDDR of 2.525 was estimated based on extrarespiratory effects (RBC cholinesterase inhibition) in Sprague Dawley rats (bodyweight = 267g). The MMAD and GSD of 2.57 and 3.785 µm, respectively, at 0.05 mg/L were used to derive the RDDR.

The HECs are summarized in Table 4.6.4.3, as well as human equivalent doses (HEDs) calculated for residential and occupational handler scenarios. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

A total uncertainty factor of 300X is appropriate for inhalation exposures (3X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF for residential assessments or a 10X database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)).

### 4.6.2 Recommendations for Combining Routes of Exposure for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major routes (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the oral, dermal, and inhalation routes are all derived from RBC cholinesterase inhibition. Thus, all routes can be combined.

### 4.6.3 Cancer Classification and Risk Assessment Recommendation

TCVP is classified as a Group C, possible human carcinogen, based on statistically significant increases in combined hepatocellular adenoma/carcinoma (primarily carcinomas) in the female B6C3F1 mouse, suggestive evidence of thyroid c-cell adenomas, and adrenal pheochromocytomas in the rat, as well as mutagenicity concerns. Following a reassessment of the mutagenicity data available on TCVP, it was determined that the relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[12]. A cancer potency factor ($Q_1{}^*$) of $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$ was estimated using the Weibull 83 time-to-tumor model. A 3/4 body weight scaling factor was used to convert from mouse to human equivalents. Following the submission and review of the required assays, the need for an updated cancer assessment will be determined.

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[12] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

### 4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

See Tables 4.6.4.1, 4.6.4.2, and 4.6.4.3 below.



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| Table 4.6.4.1. Summary of Toxicological Doses and Endpoints for TCVP for Use in Dietary and Non-Occupational Human Health Risk Assessments | | | | |
|---|---|---|---|---|
| **Exposure/ Scenario** | **Point of Departure** | **Uncertainty Factors*** | **Level of Concern for Risk Assessment** | **Study and Toxicological Effects** |
| Acute Dietary (all populations, except adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Acute RfD = 0.028 mg/kg/day<br>aPAD = 0.0028 mg/kg/day | Acute dose CCA study (MRID 48773401a) – Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND11 and 21 male and female RBC AChE inhibition |
| Acute Dietary (Adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 1x | Acute RfD = 0.028 mg/kg/day<br>aPAD = 0.028 mg/kg/day | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Steady State Dietary (all populations, except adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Steady State RfD = 0.028 mg/kg/day<br>ssPAD = 0.0028 mg/kg/day | Acute dose CCA study (MRID 48773401a) – Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Steady State Dietary (Adults 50-99) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 1x | Steady State RfD = 0.028 mg/kg/day<br>ssPAD = 0.028 mg/kg/day | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Incidental Oral (steady state) | $BMDL_{10}$ = 2.8 mg/kg/day | $UF_A$= 10x<br>$UF_H$=10x<br>FQPA SF = 10x | Residential LOC for MOE = 1000 | Acute dose CCA study (MRID 48773401a) - Rat<br><br>$BMD_{10}$ = 3.2 mg/kg/day, based on PND 11 and 21 male and female RBC AChE inhibition |
| Dermal (steady state) | No potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day and no concern for quantitative susceptibility. | | | |

| | | | | |
|---|---|---|---|---|
| Inhalation (steady state) | $BMDL_{10}$=0.022 mg/L/day (males) | $UF_A$= 3x<br>$UF_H$=10x<br>FQPA SF = 10X | Residential LOC for MOE = 300 | Subchronic Inhalation Toxicity Study (MRID 48803501) – Rat<br><br>$BMD_{10}$ = 0.12 mg/L/day, based on RBC AChE inhibition in both sexes |
| Cancer (oral, dermal, inhalation) | Classification: A possible human (Group C) carcinogen. $Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$ | | | |

[1] **Explanation of Abbreviations:** Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies); MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. AChE = acetylcholinesterase. $BMDL_{10}$= benchmark dose lower limit for 10% response. PAD = population adjusted dose. (a = acute. ss = steady state or maximal AChE inhibition.

*The 10X FQPA SF is retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 for which the FQPA SF has been reduced to 1X.

**Table 4.6.4.2 Summary of Toxicological Doses and Endpoints for TCVP for Use in Occupational Human Health Risk Assessments**

| Exposure/ Scenario | Point of Departure | Uncertainty Factors | Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Dermal (steady state) | No potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day and no concern for quantitative susceptibility. | | | |
| Inhalation (steady state) | $BMDL_{10}$=0.022 mg/L/day (males) | $UF_A$= 3x<br>$UF_H$=10x<br>$UF_{DB}$= $10x^A$ | Occupational LOC for MOE = 300 | Subchronic Inhalation Toxicity Study (MRID 48803501) - Rat<br><br>$BMD_{10}$ = 0.12 mg/L/day, based on RBC AChE inhibition in both sexes |
| Cancer (oral, dermal, inhalation) | Classification: A possible human (Group C) carcinogen. $Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$ | | | |

[1] **Explanation of Abbreviations:** Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UFA = extrapolation from animal to human (interspecies). UFH = potential variation in sensitivity among members of the human population (intraspecies); $UF_{DB}$ = database uncertainty factor; MOE = margin of exposure. LOC = level of concern. RBC = red blood cell. $BMDL_{10}$= benchmark dose lower limit for 10% response. AChE = acetylcholinesterase. SS = steady state or maximal AChE inhibition which occurs around 2-3 weeks for OPs and is a specific exposure assessment conducted

for OPs instead of the traditional short, intermediate, or chronic assessments. The SS assessment is protective of longer durations including chronic.
[A] The 10X database uncertainty factor applies to occupational worker assessment to account for potentially pregnant workers due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5).

**Table 4.6.4.3 Summary of HEC/HED Values for TCVP**

| Population | Scenario | Tox Duration Adjustment | | HEC | | HED |
|---|---|---|---|---|---|---|
| | | hours/day[a] | days/week[b] | mg/L | mg/m$^3$ | mg/kg/day |
| Occupational | Handler | 0.75 | 1 | 0.042 | 41.663 | 3.94 |
| Residential | Handler | | | 0.056 | 55.550 | 1.31 |
| | Bystander | 0.25 | 0.714 | 0.010 | 9.920 | |

HEC = human-equivalent concentration; HED = human-equivalent dose. See Appendix C for details.
HEC = rat POD × daily duration adjustment × weekly daily duration adjustment × RDDR.
HED = HEC × human-specific conversion factor (11.8 L/hr/kg) × daily duration.
[a] hours of exposure [animal study (6 hours) ÷ human worker (8 hours) or bystander (24 hours)]
[b] days of exposure [animal study (5 days/week ÷ bystander (7 days/week)/human worker (5 days/week)]

## 4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for TCVP, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), TCVP is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[13] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. TCVP is on List 1 for which EPA has received all the required Tier 1 assay data. The agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[14].

## 5.0 Dietary Exposure and Risk Assessment

## 5.1 Metabolite/Degradate Residue Profile

### 5.1.1 Summary of Plant and Animal Metabolism Studies

Residue Chemistry Memo: DP# 243528, 3/11/98, D. Miller
Residue Chemistry Memo: DP# 206721, 9/21/94, D. Miller (Addendum to RED)
Residue Chemistry Chapter to Tetrachlorvinphos RED (DP# 199644, 7/6/94, F. Suhre)
Residue Chemistry Memo: J. Abbotts, No DP#, 4/93, Results of Metabolism Committee Meeting

There are no registrations or tolerances for plant commodities, so plant metabolism studies are not required for TCVP. The qualitative nature of the residue in ruminants following oral or dermal dosing, and in poultry following dermal application, is adequately understood based on previously submitted studies. The HED Metabolism Committee (9/8/93 Meeting) has determined that the residues of concern for tolerance enforcement and for risk assessment for carcinogenicity are the parent compound and four metabolites: tetrachlorvinphos, des-O-methyl tetrachlorvinphos, 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms), 2,4,5-trichloroacetophenone, and 1-(2,4,5-trichlorophenyl)ethanediol. For the non-cancer risk assessment for cholinesterase inhibition, tetrachlorvinphos is the only residue of concern.

### 5.1.2 Summary of Environmental Degradation

Drinking Water Assessment Memo (EFED): DP# 419448, 11/6/14, C. Peck[15]

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[13] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of
chemicals.
[14] http://www.epa.gov/endo/
[15] C. Peck, 11/6/2014, D419448, Tetrachlorvinphos (TCVP) Drinking Water Assessment for Registration Review



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TCVP is moderately mobile in soil and not stable in terrestrial or aquatic environments. The TCVP degradates appear to be as mobile, and in most cases more mobile, than the parent. TCVP is soluble in water at up to 11.6 mg/L, and is not expected to volatilize significantly due to a low vapor pressure of 2.6 x $10^{-7}$ torr (25°C). The compound is hydrophobic (Log $K_{ow}$ of 3.53). TCVP hydrolyzes in water at a pH-dependent rate. Hydrolysis is relatively rapid in alkaline water (half-life of 10.3 days at pH 9). In neutral to acidic water (pH 5 to 7), TCVP hydrolyzes with slower half-lives of 30 to 57 days. A major degradate of hydrolysis found in the aqueous solution at pH 9 was des-O-methyl tetrachlorvinphos (28% at Day 21). Hydrolysis rates for the TCVP Total Residue of Concern (TRC) could not be calculated, as not all degradates in the study extracts were identified; therefore, TCVP TRC was considered stable to hydrolysis.

TCVP isomer mixture (50:50, Z:E) readily biodegraded in aerobic soils, with a half-life of approximately 9 days. However, the rate of biodegradation for the mixed isomer of the parent TCVP was slightly reduced as concentrations decreased, which may indicate that one isomer degrades more rapidly than the other. Major soil degradates include TCPEol, TCCEol, TCPEone and TCBA. The TCVP TRC that were identified in the aerobic soils biodegraded with half-lives of from 53 to 200 days.

### 5.1.3 Comparison of Metabolic Pathways

Metabolism in ruminants (dermal and oral administration; tissue), poultry (oral; tissue) and rats (oral; excreta) is similar, generally resulting in parent TCVP and the four metabolites of concern (TCVPdeme, TCPEdiol, TCPEone and TCPEol). However, the metabolite TCPEone was not found in detectable levels in the rat metabolism study and the metabolite TCPEdiol was not detected in the goat studies. Unchanged parent TCVP was found in the goat dermal study, but was not detected in the goat oral study.

### 5.1.4 Residues of Concern Summary and Rationale

The HED Metabolism Committee (9/8/93 Meeting) has determined that the total residues of concern (TRC) for carcinogenicity are the parent compound tetrachlorvinphos and metabolites which, like tetrachlorvinphos, contain the 2,4,5 trichlorobenzene ring. For livestock commodities, the total residues of concern for carcinogenicity are tetrachlorvinphos [TCVP] plus the following four metabolites: des-O-methyl tetrachlorvinphos [TCVPdeme]; 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms) [TCPEol]; 2,4,5-trichloroacetophenone [TCPEone]; and 1-(2,4,5-trichlorophenyl)ethanediol [TCPEdiol]. For drinking water carcinogenicity assessment, the total residues of concern include the four aforementioned metabolites for livestock plus 2 additional degradates: 1-(2,4,5-trichlorophenyl)-2-chloroethanol [TCCEol], and 2,4,5-trichlorobenzoic acid [TCBA].

For the non-cancer risk assessment for cholinesterase inhibition, TCVP is the only residue of concern. For tolerance enforcement the residues of concern include TCVP plus, TCVPdeme, TCPEdiol, TCPEone and TCPEol.

See Appendix E for a table of parent and metabolite structures and chemical properties.

| Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression | | | | |
|---|---|---|---|---|
| **Matrix** | | **Residues included in Risk Assessment (Cholinesterase Inhibition)** | **Residues included in Risk Assessment (Carcinogenicity)** | **Residues included in Tolerance Expression** |
| Plants | Primary Crop | NA | NA | NA |
| | Rotational Crop | NA | NA | NA |
| Livestock | Ruminant | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol |
| | Poultry | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol |
| Drinking Water | | TCVP | TCVP, TCVPdeme, TCPEdiol, TCPEone and TCPEol, TCCEol, TCBA | NA |

NA= not applicable
TCVP= tetrachlorvinphos
TCVPdeme,= des-O-methyl tetrachlorvinphos
TCPEol= 1-(2,4,5-trichlorophenyl)ethanol (free and conjugated forms)
TCPEone= 2,4,5-trichloroacetophenone
TCPEdiol= 1-(2,4,5-trichlorophenyl)ethanediol
TCCEol =l-(2,4,5-trichlorophenyl)-2-chloroethanol
TCBA =2,4,5-Trichlorobenzoic acid

## 5.2 Residue Chemistry and Food Residue Profile

Residue Chemistry Memo: D243528, 3/11/98, D. Miller

*Residue Chemistry*

Tolerances are established for residues of TCVP in animal commodities since residues may occur in milk, eggs, meat, fat, or meat byproducts as a result of the registered uses on livestock (oral and dermal uses) and around livestock premises. There are no registered uses on plant (including feedstuffs) commodities. This section provides the background and current status of residue chemistry requirements for TCVP and includes residue data submitted and reviewed since the 1994 Residue Chemistry Chapter of the TCVP RED and the 2006 TCVP RED.

The 1994 Residue Chemistry Chapter cited the need for the following magnitude of the residue studies: *New magnitude of the residue studies reflecting oral and dermal exposure of beef cattle, dairy cattle, and hogs, and dermal exposure of poultry to tetrachlorvinphos are required. All residues of concern should be analyzed in cattle, hogs, and poultry using validated analytical methods.*

Subsequent to the TCVP RED, in 2007, residue studies on cattle (dermal and oral treatments; MRID 47193001) and poultry (dermal treatment; MRID 47193001) were submitted, as was a companion storage stability study (MRID 47193001) and a residue analytical method (MRID 47369201). Those studies were reviewed under DP #s D320848, D320858, D320859, and D381350 (C. Olinger, 10/7/10, *Tetrachlorvinphos. Cattle Oral/Dermal and Poultry Dermal Studies. Summary of Residue Data Submitted in Support of Reregistration*). The submitted magnitude of the residue studies on cattle and poultry were determined to be inadequate, but upgradeable pending submission of supporting storage stability data. The companion storage stability study was determined to be unacceptable because of study design. Additional information was also requested regarding the maximum storage duration of all samples collected from both the cattle and poultry studies. In 2011, additional information (MRIDs 486378101 and 48319001) pertaining to the storage stability deficiencies was submitted and reviewed (C. Olinger, 3/25/11, D385359 and D386954, *Tetrachlorvinphos. Response to Comment on Storage Stability Residue Data Deficiencies)*. The poultry and cattle residue data (860.1480) deficiencies are now fulfilled and no further data are being required.

In response to the data requirement for a residue study in hogs, a waiver request was submitted and granted in 2011 (C. Olinger, 4/25/11, D320857, *Tetrachlorvinphos. Request for Waiver of a Swine Magnitude of Residue Study).* It was determined that TCVP residues in swine tissues are not likely to be higher than the residues in ruminants and that ruminant data may be translated to swine. The conclusion was based on the poor oral and dermal absorption of TCVP in livestock and the fact that residence time in swine intestines is significantly shorter relative to that in a ruminant. No additional residue data (860.1480) on hogs are being required.

In response to a TCVP Generic Data Call-In (GDCI) issued 12/29/09, data were submitted evaluating TCVP metabolites using the FDA Multiresidue Methods Test guidelines in Pesticide Analytical Manual (PAM) Vol. I (MRID 48655201) and were reviewed 7/5/12 (D. Drew, D396833, *Tetrachlorvinphos (TCVP). Multiresidue Methods (MRM) Study of the Metabolites of TCVP*). The data requirement for MRM testing (860.1360) has been fulfilled.

The registrant submitted a proposed method SCR/006 for tolerance enforcement of livestock commodities that includes detection of TCVP and the metabolites TCVPdeme, TCPEol, TCPEone and TCPEdiol (MRID 47369201, 2007). The HED review (D320848, D320858, D320859, and D381350) determined that the method was adequate, but that an independent laboratory validation (ILV) trial remained outstanding. A Generic Data Call-In (GDCI) for an ILV was originally issued December 29, 2009. A different proposed method (Method 14020.6106) and an associated ILV study (Method 14020.6107) were subsequently submitted to the agency (MRID 49419301, 2015). Because the proposed Method 14020.6106 monitors only a single ion transition for each analyte, alternative confirmatory procedures are necessary; the previously submitted method SCR/006 (MRID 47369201) is considered acceptable as a confirmatory method. The analytical method test data for 14020.6106 are classified as scientifically acceptable for use as an analytical method for ruminant and poultry commodities.

*Food Residue Profile*

The available magnitude of the residue study for dairy cattle reflect a combination of two treatments: oral administration of tetrachlorvinphos for 29-31 days at actual rates of 1.51-1.55 and 4.63 g ai/750 kg BW per day (6.3-6.5x and 19.3x, respectively, the maximum registered rate of 0.24 g ai/750 kg BW for feed-through treatment) and dermal spray treatments on three occasions, at ~14 day intervals, at actual rates of 10.11 and 19.2-19.5 g ai per animal per dose (~0.5 and 1.0x, respectively, the maximum registered rate of 18.9 g ai/animal for direct animal spray treatment). At the combined treatment regime (6.5x dermal spray plus 1x oral treatment), the maximum total residues of concern (with the maximum residues of the parent in parentheses) were: 0.072 (0.036) ppm for milk, 0.078 (<0.01) ppm for cream, 0.158 (<0.01) ppm for liver, 0.278 (0.015) ppm for kidney, 0.272 (0.212) ppm for muscle, 0.842 (0.558) ppm for subcutaneous fat, and 0.747 (0.340) ppm for peritoneal fat.

The available magnitude of the residue study for poultry reflects 6-7 dermal spray treatments of laying hens with an EC formulation, made at two-week retreatment intervals, at 0.0908, 0.182, or 0.545 g ai/hen/application. These application rates, respectively, correspond to ~0.5x, 1.0x, or 2.9x the maximum registered direct spray treatment rate of 0.19 g ai/bird daily. At ~1.0x, the maximum total residues of concern (with the maximum residues of the parent in parentheses) were: 0.288 (0.026) ppm for egg, 0.517 (0.016) ppm for liver, 0.583 (0.022) ppm for kidney, 0.396 (0.082) ppm for muscle, 19.405 (6.030) ppm for skin with fat, and 1.298 (0.099) ppm for abdominal fat.

There were no detectable residues of parent TCVP in the most recent USDA PDP monitoring data for beef meat, liver, or fat, or for milk and cream; nor were there detectable residues in pork fat. There were no detectable residues in chicken meat or liver. There was one detectable residue in egg just above the method limit of detection (LOD; 742 samples). PDP did not analyze chicken fat or skin for TCVP. The TCVP metabolites of concern for cancer assessment were not measured by PDP.

## 5.3 Water Residue Profile

Drinking Water Assessment Memo (EFED): D419448, 11/6/14, C. Peck

The Surface Water Concentration Calculator (SWCC) computer model was used to generate surface water Estimated Drinking Water Concentrations (EDWCs) for use in the human health dietary risk assessment, while the PRZM-GW and SCI-GROW models were used to generate groundwater EDWCs. The residues of concern for acute and steady state dietary exposure included cholinesterase-inhibiting compounds, which were determined to be TCVP parent only. For carcinogenicity, (total) residues of concern (TRC) included TCVP and the following metabolites which, like TCVP, contain the 2,4,5 trichlorobenzene ring: des-O-methyl tetrachlorvinphos,1-(2,4,5-trichlorophenyl)ethanediol, TCPEol (1-(2,4,5-trichlorophenyl)ethanol), TCPEone (2,4,5-trichloroacetophenone), TCCEol (l-(2,4,5-trichlorophenyl)-2-chloroethanol), and TCBA (2,4,5-trichlorobenzoic acid).

Maximum EDWCs (based on maximum labeled usage for kennels, poultry droppings, garbage and manure piles, and corrals) for TCVP residues in surface water and groundwater for dietary assessment are presented in Table 5.3. Daily time series outputs for the thirty year simulation were also provided to HED for use in dietary exposure modeling.

This dietary assessment used the maximum total residues of concern (TRC) EDWC of 22.4 ug/L for the cancer analysis, input as a single point estimate. For the selected drinking water scenarios, a distribution of surface water residues was used probabilistically in the dietary model for non-cancer assessments based on cholinesterase inhibition. The following paragraph describes the derivation of those distributions.

Daily time-series outputs that simulate 29 years (1962-1990) of residues of TCVP in surface drinking water for the outdoor uses (on kennels, poultry droppings, garbage and manure piles, and corrals) were modeled using the SWCC. No further adjustments were made to the acute distribution files, but since the steady state average dietary assessments use 21-day forward rolling averages for drinking water, the steady state distributions were further adjusted to be 21-day forward rolling averages. In the 21-day rolling average distributions, the first data point is the average of days 1-21, the second data point is the average of days 2-22, the third data point is the average of days 3-23, etc. The 21-day rolling average continues until the last 20 days of residues of the final distribution year.

**Table 5.3 Summary of Estimated Surface Water and Groundwater Concentrations for Tetrachlorvinphos**

| DRINKING WATER SOURCE (MODEL USED) | MAXIMUM ESTIMATED DRINKING WATER CONCENTRATION (EDWC) | |
|---|---|---|
| | Acute (µg/L) (TCVP only) | Cancer (µg/L) (TRC) |
| Surface water (SWCC) | **4.03** | 4.11 |
| Groundwater (PRZM-GW) | $8.54 \times 10^{-5}$ | **22.4** |
| Groundwater (SCI-GROW) | $5.61 \times 10^{-3}$ | $7.36 \times 10^{-2}$ |

* EDWCs based on maximum labeled usage for kennels, poultry droppings, garbage and manure piles, and corrals.

## 5.4 Dietary Risk Assessment

Dietary Assessment Memo: D436835, 9/20/2016, D. Drew[16]

[16] D. Drew, 9/20/2016, Tetrachlorvinphos (TCVP). Revised Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment, D436835.

The previous dietary risk assessment for tetrachlorvinphos was conducted on 10/29/2014 (D. Drew, D426985, *Tetrachlorvinphos (TCVP) Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment*). That assessment has been updated in D436835 (D. Drew, 9/20/2016, Tetrachlorvinphos (TCVP). *Revised Acute, Steady State, and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Human Health Risk Assessment*) to reflect changes in the toxicological PODs for the acute and steady state dietary exposures. In addition, minor corrections have been made based on comments received on the 2014 dietary assessment (MRID 4989101, Bayer CropScience, *Comments to EPA's "Tetrachlorvinphos (TCVP) Human Health Draft Risk Assessment for Registration Review", Docket ID: EPA-HQ-OPP-2008-0316*).

### 5.4.1 Description of Residue Data Used in Dietary Assessment

HED has conducted acute, steady state, and cancer dietary (food and drinking water) exposure and risk assessments using DEEM version 3.16 for TCVP.

The dietary exposure analyses for TCVP are refined. The only food forms included in the analyses are based on animal commodities. The food residues were based upon U. S. Department of Agriculture's Pesticide Data Program (USDA PDP) monitoring data except in a couple of instances where no appropriate PDP data were available (i.e., high-end residues from poultry dermal studies were used for poultry fat and poultry skin). The Biological and Economic Analysis Division (BEAD) of OPP provided percent livestock treated information. Model-derived estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effect Division (EFED). EDWCs were based on spot applications to kennels, poultry droppings, garbage and manure piles, and corrals and were directly incorporated into the assessments as described in Section 5.3 above.

Since the PDP only analyzed for residues of TCVP (and not for TCVP metabolites) a factor was applied to the PDP residues in order to account for all the metabolites of concern for the cancer assessment. The factor was calculated by determining the ratio of parent TCVP to total residues of concern in the livestock residue studies (see Table 2, D436835).

### 5.4.2 Percent Crop Treated Used in Dietary Assessment

For the acute and steady state analyses, the maximum estimated percent livestock treated of 3% was used for cattle and swine and the estimated maximum of 11% was used for poultry.

For the cancer analysis, the following estimated average percent livestock treated values were used: 1% for dairy cattle, 2% for beef cattle and swine, and 6% for poultry.

### 5.4.3 Acute Dietary Risk Assessment

The refined acute dietary (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the acute population adjusted dose (aPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 190% of the aPAD.

When drinking water is analyzed by itself, the acute dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95th and 99.9th percentile of exposure.

Most of the exposure from food is due to the high-end residue on chicken skin from poultry dermal studies (residue on uncooked chicken skin from direct dermal spray applications at maximum labeled rates with a 0-day pre-slaughter interval).

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

**Table 5.4.3.1. Results of Acute Dietary (Food Only) Exposure and Risk Analysis.**

| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.0028 | 0.000022 | < 1 | 0.000680 | 24 | 0.002806 | 100 |
| All Infants (<1 year old) | 0.0028 | 0.000012 | < 1 | 0.000288 | 10 | 0.002739 | 98 |
| Children 1-2 years old | 0.0028 | 0.000069 | 2.5 | 0.001073 | 38 | 0.004708 | 170 |
| **Children 3-5 years old** | 0.0028 | 0.000054 | 1.9 | 0.001386 | 50 | 0.005230 | 190 |
| Children 6-12 years old | 0.0028 | 0.000037 | 1.3 | 0.000938 | 33 | 0.003941 | 140 |
| Youth 13-19 years old | 0.0028 | 0.000024 | < 1 | 0.000731 | 26 | 0.003318 | 120 |
| Adults 20-49 years old | 0.0028 | 0.000022 | < 1 | 0.000722 | 26 | 0.002584 | 92 |
| Adults 50-99 years old | 0.028 | 0.000011 | < 1 | 0.000492 | 1.8 | 0.001690 | 6.0 |
| Females 13-49 years old | 0.0028 | 0.000020 | < 1 | 0.000651 | 23 | 0.002300 | 82 |

[1] Population with the greatest exposure is in bold.
[2] aPAD = acute population-adjusted dose.

**Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only) Exposure and Risk Analysis.**

| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
|---|---|---|---|---|---|---|---|
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| General U.S. Population | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000121 | 4.3 |
| **All Infants (<1 year old)** | 0.0028 | 0.000022 | < 1 | 0.000093 | 3.3 | 0.000369 | 13 |
| Children 1-2 years old | 0.0028 | 0.000012 | < 1 | 0.000048 | 1.7 | 0.000187 | 6.7 |

| Table 5.4.3.2. Results of Acute Dietary (Drinking Water Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | aPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD | Exposure (mg/kg/day) | % aPAD |
| Children 3-5 years old | 0.0028 | 0.000011 | < 1 | 0.000041 | 1.4 | 0.000147 | 5.2 |
| Children 6-12 years old | 0.0028 | 0.000008 | < 1 | 0.000030 | 1.1 | 0.000111 | 4.0 |
| Youth 13-19 years old | 0.0028 | 0.000006 | < 1 | 0.000025 | < 1 | 0.000095 | 3.4 |
| Adults 20-49 years old | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000118 | 4.2 |
| Adults 50-99 years old | 0.028 | 0.000009 | < 1 | 0.000032 | < 1 | 0.000110 | < 1 |
| Females 13-49 years old | 0.0028 | 0.000009 | < 1 | 0.000033 | 1.2 | 0.000120 | 4.3 |

[1] Population with the greatest exposure is in bold.
[2] aPAD = acute population-adjusted dose.

### 5.4.4 Steady State Dietary Risk Assessment

The refined steady state (food only) exposure analysis resulted in risk estimates above HED's level of concern (exceeded 100% the steady state population adjusted dose (ssPAD)) at the 99.9th percentile of exposure for the children's population subgroups. The highest exposed subgroup is children 3-5 years old at 120% of the ssPAD.

The steady state dietary (water only) risk estimates are all below HED's level of concern for the U.S. population and all population subgroups at the 95th and 99.9th percentile of exposure.

Most of the exposure from food is due to the high-end residue on chicken skin from poultry dermal studies (residue on uncooked chicken skin from direct dermal spray applications at maximum labeled rates with a 0-day pre-slaughter interval).

Since dietary exposures from food alone were of concern, drinking water exposures were not combined with exposures from food. Combining those exposures would result in even greater risk estimates of concern.

| Table 5.4.4.1. Results of Steady State Dietary (Food Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| General U.S. Population | 0.0028 | 0.000092 | 3.3 | 0.000599 | 21 | 0.001994 | 71 |
| All Infants (<1 year old) | 0.0028 | 0.000020 | < 1 | 0.000299 | 11 | 0.001843 | 66 |
| Children 1-2 years old | 0.0028 | 0.000128 | 4.6 | 0.001070 | 38 | 0.003181 | 110 |
| **Children 3-5 years old** | 0.0028 | 0.000152 | 5.4 | 0.001214 | **43** | **0.003444** | **120** |
| Children 6-12 years old | 0.0028 | 0.000130 | 4.6 | 0.000782 | 28 | 0.002991 | 110 |
| Youth 13-19 years old | 0.0028 | 0.000116 | 4.1 | 0.000645 | 23 | 0.002118 | 76 |
| Adults 20-49 years old | 0.0028 | 0.000112 | 4.0 | 0.000621 | 22 | 0.001971 | 70 |

| Table 5.4.4.1. Results of Steady State Dietary (Food Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| Adults 50-99 years old | 0.028 | 0.000049 | < 1 | 0.000418 | 1.5 | 0.001105 | 3.9 |
| Females 13-49 years old | 0.0028 | 0.000098 | 3.5 | 0.000572 | 20 | 0.001481 | 53 |

[1] Population with the greatest exposure is in bold.
[2] ssPAD = steady state population-adjusted dose.

| Table 5.4.4.2. Results of Steady State Dietary (Drinking Water Only) Exposure and Risk Analysis. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Population Subgroup[1] | ssPAD[2] (mg/kg/day) | 95th Percentile | | 99th Percentile | | 99.9th Percentile | |
| | | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD | Exposure (mg/kg/day) | % ssPAD |
| General U.S. Population | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000096 | 3.4 |
| **All Infants (<1 year old)** | 0.0028 | 0.000024 | < 1 | 0.000088 | 3.2 | 0.000300 | 11 |
| Children 1-2 years old | 0.0028 | 0.000013 | < 1 | 0.000045 | 1.6 | 0.000143 | 5.1 |
| Children 3-5 years old | 0.0028 | 0.000011 | < 1 | 0.000038 | 1.4 | 0.000114 | 4.1 |
| Children 6-12 years old | 0.0028 | 0.000008 | < 1 | 0.000028 | < 1 | 0.000085 | 3.0 |
| Youth 13-19 years old | 0.0028 | 0.000007 | < 1 | 0.000023 | < 1 | 0.000075 | 2.7 |
| Adults 20-49 years old | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000094 | 3.4 |
| Adults 50-99 years old | 0.028 | 0.000009 | < 1 | 0.000030 | < 1 | 0.000087 | < 1 |
| Females 13-49 years old | 0.0028 | 0.000009 | < 1 | 0.000031 | 1.1 | 0.000095 | 3.4 |

[1] Population with the greatest exposure is in bold.
[2] ssPAD = steady state population-adjusted dose.

### 5.4.5 Cancer Dietary Risk Assessment

The refined cancer dietary (food and drinking water) assessment resulted in an estimated exposure to TCVP and its metabolites containing the 2,4,5 trichlorobenzene moiety (the residues of concern for cancer) of 0.000513 mg/kg/day. Applying the $Q_1$* of 0.00183 $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of $9 \times 10^{-7}$. Drinking water is the major contributor to the cancer dietary risk estimate.

| Table 5.4.5.1. Summary of CANCER Dietary Exposure and Risk for Tetrachlorvinphos (and metabolites). | | | | | | |
|---|---|---|---|---|---|---|
| Population Subgroup | Food and Water | | Food Only | | Water Only | |
| | Exposure (mg/kg/day) | Risk | Exposure (mg/kg/day) | Risk | Exposure (mg/kg/day) | Risk |
| Adults | 0.000513 | $9 \times 10^{-7}$ | 0.000044 | $8 \times 10^{-8}$ | 0.000469 | $8 \times 10^{-7}$ |

## 6.0 Residential and Non-Occupational Exposure/Risk Characterization

Occupational and Residential Exposure Memo: D436833, 12/21/2016, W. Britton [17]

Residential exposures (handler and post-application) are anticipated from the use of TCVP pet products for dogs and cats including collars, dusts/powders, and pump/trigger sprays. Exposures are expected for adults who apply TCVP products to their pets and from post-application exposures for adults and children who may contact previously treated pets. Residential TCVP handler and post-application exposures are anticipated to be short- (1 to 30 days), intermediate- (1 to 6 months), and long-term (>6 months – *for pet collar scenarios only*). However, because of the steady state AChE inhibition exhibited by the OPs, steady state (typically 21 days and longer for OPs, but 1 day for TCVP) residential exposures were assessed for TCVP pet products.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

Following EPA's December 21, 2015 Draft TCVP risk assessment, Bayer HealthCare, Hartz Mountain Corporation, and NRDC submitted comments during the public comment period, primarily regarding the formulation type of pet collars. This document addresses, where appropriate, those comments. A comprehensive response to comments on the TCVP draft human health risk assessment (including ORE-specific comments) is also provided in the following memo: D. Drew et al., Tetrachlorvinphos (TCVP) Health Effects Division Response to Comments on the December 21, 2015 Draft Human Health Risk Assessment for TCVP Registration Review, D433403, 12/21/2016.

Formulation Type Issue: In 2009, the Natural Resources Defense Council (NRDC) petitioned the EPA to cancel all pet uses for the pesticide tetrachlorvinphos (TCVP). In 2014, the agency responded to the 2009 petition by conducting a human health risk assessment for all currently registered TCVP products which include collars, dusts/powders, and pump and trigger spray formulations. That risk assessment was dated Nov. 5, 2014. At that time, no human health risks of concern were identified for any TCVP pet product, and the petition to cancel all pet products was denied on Nov. 6, 2014. The NRDC subsequently responded to the agency's denial with arguments presented in NRDC's Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.) (Opening Brief). Among the arguments raised by NRDC was the assertion that the agency incorrectly considered the TCVP flea collar formulation to be a liquid formulated product:

*"NRDC states that the EPA failed to 'research' the TCVP flea collar label; instead it ignored the information in the label right on the box regarding the chemical formulation.' [NRDC Opening*

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[17] W. Britton *et al.*, 12/21/2016, D436833, Tetrachlorvinphos: Final Occupational and Residential Exposure Assessment for Registration Review

*Brief, p.67]. The label for the Hartz UltraGuard Flea and Tick Collar for Dogs (EPA Reg. No. 2596-84) states that 'as the collar begins to work, a fine white powder will appear on the surface.' As a result, NRDC argues that the transfer coefficient (TC) recommended for solid formulations should have been used instead of the transfer coefficent for liquid formulations as is recommended by the 2012 Residential SOPs."*[18]

The agency responded to this and all other arguments raised by NRDC in a December 21, 2015 memorandum,[19] issued along with the Draft risk assessment for Registration Review. The following is an excerpt of the agency's response relating to the pet collar formulation issue:

*"Per EPA's 2012 Residential SOPs*[20]*: Treated Pets, pet collar products are categorized as a liquid formulation. This position was based on research conducted at the time of SOP development that supported that pet collars function by means of diffusion, transferring from the collar to the surrounding area. More specifically, the active ingredient, which is embedded in the collar matrix, diffuses slowly through the matrix, thus controlling the amount of the active ingredient at the collar's surface. The active ingredient available on the surface of the pet collar then "rubs off" or transfers from the collar to the animal's hair coat via embedded lubricants which function as transfer agents at the surface of the collar. Based on the categorization of pet collars as liquid formulations, the assessment of post-application exposures for these product types would be conducted with use of the TCs, and the fraction active ingredient on the hands from TC studies ($Fai_{hands}$) recommended for the assessment of liquid formulated products as recommended in the 2012 Residential SOPs.*

*The information provided by NRDC states that the label for the Hartz UltraGuard Flea and Tick Collar for Dogs (EPA Reg. No. 2596-84) states that "as the collar begins to work, a fine white powder will appear on the surface." HED has confirmed that this statement is present on the current labeling for the identified product and that an identical statement is also found on the following TCVP pet collar products (5 of 9 total pet collar products): EPA Reg. Nos. 2596-62, 2596-63, 2596-83, 2596-84, and 2596-139. Taking label statements into account, and based upon further research which suggests that some pet collars may act by extrusion of the active ingredient from the collar matrix as a fine dust, HED has reconsidered the position that the TCVP pet collars are all liquid formulated products. As a result of this uncertainty, in the TCVP draft human health risk assessment in support of registration review, HED has updated the assessment of post-application risks from TCVP pet collars in consideration of both the dust- and liquid-specific TCs and $Fai_{hands}$ recommended SOP values."*[21]

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[18] W. Britton. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589, at 8 (summarizing NRDC's argument).

[19] *Id.*

[20] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[21] *Id.* at 8-9.

In response to the 2015 Draft TCVP risk assessment, Bayer HealthCare submitted comments to address the formulation type issue. Bayer agreed with the approach employed by the agency, stating: "*Based on the NRDC assertion and the statement on the collar packaging the agency has taken the understandable approach of calculating the post-application exposure, using both liquid and solid formulation transfer coefficients, until the uncertainty is resolved.*" Bayer proceeded to address the formulation type issue by describing how the active ingredient is released from the collar and distributed on the animal. Bayer described that, "*To achieve their goal of effective pest control, the flea collars are designed to deliver the insecticide from the collar in either a liquid or solid state. The collar is made from a mixture of plastic resins and resin modifiers. The resins are formulated to have appropriate strength and flexibility so the collar can withstand the shaping operations without cracking or crumbling. The resins must also have appropriate release characteristics, such that the TCVP (or other insecticide active ingredient) can escape the collar at the proper rate, while inert components remain in the collar.*"

Per Bayer, TCVP is distributed on the animal by abrasion or movement against the animal or diffusion from the animal's body heat. "*Within a few days after manufacture, the insecticide begins to migrate from within the body of the collar and form a coating of particles, resembling a dust or powder on the surface of the collar. As the particles of the active ingredient are displaced or shaken from the surface due to the normal activity of the animal, additional particles appear by migration from the body of the composition to replace the insecticide particles displaced from the surface (i.e., the displaced particles are replenished continuously). This describes the typical release mechanism and explains the presence of the powder as raised by NRDC. The powders are in the immediate vicinity of the collar; however, this is not necessarily the form in which the insecticide is dispersed to the animal or relevant to the transfer coefficient.*" They continued to describe that the sebaceous glands within the dog's skin that lubricate the hair are the mechanism for dispersion of the insecticide. "*Insecticides that are used in flea collars are lipophilic and soluble in the animal's skin oils. So, even though the collars may release some of the insecticides as a solid they are dispersed along the animal's body as a solution or suspension in the animal's skin via the natural skin oils.*" As such, the assessment of human health risks from TCVP pet collars were conducted in a manner that accounts for the likelihood of the presence of both liquid and solid forms while considering the isolated location (i.e., the head/neck) of ai in the dust/powder form.

While informative, Bayer's comments pose a dilemma for the agency. Although they describe the mechanism of dispersion of active ingredient along the animal's body as a solution or suspension in the skin, they also indicate that the insecticide begins to migrate from within the collar as a "coating of particles, resembling a dust or powder form on the surface of the collar" and that "flea collars are designed to deliver the insecticide from the collar in either a liquid or solid state." The mechanism of active ingredient dispersion via the skin alone is not adequate to describe the potential for post-application exposures. If the active ingredient is present as a liquid or particulate or dust on the surface of the pet collar, it could be transferred in either form from the collar to the pet's fur immediately surrounding and result in the potential for post-application exposures from either direct contact with the pet collar, or the surrounding fur.

Formulation Type Approach: A unique approach has been applied in order to account for the potential for exposures from the presence of TCVP to exist as both liquid and solid forms concurrently. The approach uses the same methodologies described in the 2012 Residential SOPs for assessment of residential handler and post-application exposure assessment for pet collar usage. However, whereas the 2012 Residential SOPs recommend that pet collars be assessed as a liquid formulation, the present approach assesses pet collar exposures as both a liquid and solid form. For residential handlers, this means use of the liquid UE data as recommended by the 2012 Residential SOPs and chemical-specific dust UE data for these formulation types. For the residential post-application exposure assessment, this means use of transfer coefficients (dermal exposures) and the fraction of active ingredient on hands from the transfer coefficent studies (hand-to-mouth exposures) specific to both liquid and solid formulation types.

The individual dust and liquid formulation handler and post-application doses were estimated, and then another step was included in the assessment where the liquid and dust doses were averaged assuming a ratio of liquid to dust in the collar formulation. For both handler and post-application scenarios, ratios of 1/99, 50/50, and 99/1 liquid/dust were assumed to cover a range of potential exposures.

The methodologies and inputs used for the individual formulation assessments for residential handlers and residential post-application exposures are described in Appendix B of the corresponding ORE memo (Memo, W. Britton *et al*, D436833).

Due to NRDC's argument related to the TCVP pet collar formulation, the agency has begun efforts to reevaluate pet collar formulation type to carefully consider whether pet collar products are more closely related to more traditional liquid formulation pet products such as shampoos and spot-ons, or solid formulated products such as dusts and powders. In following with this evaluation, the agency intends to request and review additional information relating to all registered pet collar products as they undergo registration review, as well as any proposed new pet collar uses. This evaluation will continue until the agency is satisfied that, based on the design and operation of pet collar products, a final formulation type decision can be made along with recommendations for human health risk assessment of exposures to pet collar-treated pets.

## 6.1 Residential Handler Exposures

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are assumed to complete all elements of an application without use of any protective equipment.

Residential handler exposures to TCVP pet products may occur via the dermal or inhalation routes while the product is placed on a cat or dog. Both steady state non-cancer and cancer residential handler exposure assessments were performed for adult homeowners applying TCVP pet collars, dusts/powders, and pump/trigger sprays products to cats and dogs. Since there is no non-cancer dermal hazard for TCVP, the steady state (non-cancer) handler assessment includes only inhalation exposures. For the cancer assessment, both dermal and inhalation exposures are

assessed.

The exposure data and assumptions that underlie the residential handler non-cancer risk estimates can be referenced in the 2014 residential assessment[22] and the 2012 Residential SOPs. The algorithms used to estimate non-cancer exposure and dose for residential handlers can be found in Appendix B of the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833) and/or the 2012 Residential SOPs.[23]

Due to the uncertainty associated with whether TCVP pet collars are liquid and/or dust formulated products, residential handler steady state inhalation exposures for TCVP pet collar application were assessed (as described above in Section 6.0) assuming pet collars could be liquid and solid (dust) formulations concurrently, with varying ratios liquid/dust. When assuming the TCVP pet collars are a liquid formulation, the liquid-specific unit exposures (UE) values (i.e., surrogate data from a spot-on applicator study) from the 2012 Residential SOPs were used. When assuming the pet collars are a solid formulation, HED used the best available data, a TCVP dust/powder applicator exposure study (MRID 45519601).

The liquid formulation spot-on surrogate UE data assumes negligible inhalation exposure; therefore, only the dust-specific UE data (i.e., a TCVP dust/powder applicator exposure study) is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates

*Pet Collars:* Because there is uncertainty whether the TCVP pet collars are liquid and/or dust formulated products, residential handler (adults) steady state inhalation exposures were evaluated assuming both liquid and solid (dust) formulations are present concurrently with varying ratios of liquid/dust. No inhalation risks of concern were identified for residential handlers for any liquid/dust formulation ratio assumption. When assuming a ratio of 1/99 liquid/dust, MOEs range from 920 to 4,600; when assuming a ratio of 50/50 liquid/dust, MOEs range from 1,800 to 9,100; and when assuming a ratio of 99/1 liquid/dust, MOEs range from 91,000 to 450,000 (LOC = 300).

*Dust/Powder and Pump/Trigger Spray*: All residential handler (adults) non-cancer steady state inhalation risks estimated for the TCVP pet dust/powder pump/trigger spray formulations are not of concern (i.e., all MOEs are > 300; LOC = 300; range = 3,200 to 160,000).

A summary of residential handler exposures and risks is presented in Appendix G.

Residential Handler Cancer Exposure and Risk Estimate Equations

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[22] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

[23] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a Lifetime Average Daily Dose (LADD) is first calculated and then compared with a $Q_1$* that has been calculated for TCVP based on dose response data in the appropriate toxicology study ($Q_1$* = 1.83 x $10^{-3}$ (mg/kg/day)$^{-1}$). Absorbed average daily dose (ADD) levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the $Q_1$* to obtain cancer risk estimates.

The exposure data and assumptions that underlie the residential handler cancer risk estimates can be found in the 2014 residential assessment[24] and the 2012 Residential SOPs. The algorithms used to estimate the LADD and cancer risk for residential handlers can be found in Appendix B of the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833).

Summary of Residential Handler Cancer Exposure and Risk Estimates

*Pet Collars:* Residential handler cancer risks (combined dermal and inhalation) estimated for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio are all $10^{-7}$. When assuming a 50/50 liquid/dust formulation ratio (use of liquid-specific and dust-specific UE data) are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$.

*Dust/Powder and Pump/Trigger Spray*: Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$.

A summary of residential handler cancer exposures and risks is presented in Appendix H.

## 6.2 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of contacting a cat/dog previously treated with TCVP pet products (dusts/powders, pump/trigger sprays, pet collars). The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenario:

1) Post-application incidental oral (hand-to-mouth) exposure (children 1 to < 2 years olds only) from contacting cats and dogs treated with TCVP.

Since there is no non-cancer dermal hazard for TCVP, a quantitative non-cancer post-application dermal exposure assessment was not performed for adults or children. A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from applications to pets.

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[24] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

The lifestages selected for each post-application scenario (i.e., children 1 to < 2 years old) are based on an analysis provided as an Appendix in the corresponding ORE assessment (Memo, W. Britton *et al.*, D436833) and the 2012 Residential SOPs.[25] While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Non-Cancer Post-Application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential non-cancer post-application risk assessment. The exposure data and assumptions that underlie the residential non-cancer post-application risk estimates can be found in the 2014 residential assessment[26] and the 2012 Residential SOPs.

Several inputs and assumptions that underlie the residential post-application risk assessment of TCVP pet products were addressed previously by EPA in the responses to NRDC's August 5, 2015 Opening Brief,[27] including: the use of the Davis study; TCVP pet collar product formulation type; daily exposure time spent in contact with TCVP treated pets; indirect hand-to-mouth activity; and the application of transferable residue data in EPA's risk assessment algorithms. NRDC has repeated all of these same arguments in its comments submitted for the 2015 DRA. EPA has addressed the use of the Davis study and TCVP pet collar product formulation type arguments herein. The agency's responses to all other arguments remain the same as addressed previously.

*Residue Transfer Assumptions:* Chemical-specific residue transfer studies were used for assessment of post-application exposures from registered TCVP pet products.

*Dust/Powder and Pump/Trigger Spray:* Consistent with the 2015 draft ORE assessment for Registration Review, a TCVP powder and pump spray study (MRID 45485501) was used to assess post-application exposure for these scenarios. A summary and discussion of the use of these data was included in the 2014 residential risk assessment. As described in the 2014 residential risk assessment, the TCVP powder and pump spray post-application exposure study was not conducted in a manner reflective of current standards that require a defined stroking procedure and greater number of petting simulations. In order to account for this difference, the agency used the maximum observed percent residue transfer on the day of product application (Day 0) for both formulations for exposure and risk quantification. Typically, the agency assesses post-application risk with use of the mean percent residue transfer measured on Day 0;

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[25] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[26] W. Britton. Residential Exposure Assessment in Response to the Natural Resources Defense Council Petition to Cancel All Pet Uses for Tetrachlorvinphos. 11/05/2014. D420283.

[27] W. Britton, Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589.

the use of the maximum value results in a more health protective risk assessment. Even though the post-application exposure study methods have evolved, the TCVP study employed a rigorous collection method and is not anticipated to underestimate exposure.

The 2012 Residential SOPs: Treated Pets recommends assessment of post-application exposures using day of application (i.e., Day 0) residue transfer -- defined as fraction application rate ($F_{AR}$) in the 2012 SOPs. Day of application (Day 0) percent residue transfer values used in the 2014 residential risk assessment for exposure/risk quantification of dusts/powders and pump/triggers sprays are as follows: dusts/powders, 0.048% (maximum observed) and pump sprays, 0.81% (maximum observed).

*Pet Collar Exposure Data Source:* The 2015 draft ORE assessment for Registration Review used both the Davis study and an amitraz pet collar residue transfer study for assessment of non-cancer residential post-application risks following contact with pets treated with TCVP pet collars. The Davis study publication was considered for use in the assessment due to arguments submitted by NRDC in its August 5th, 2015, Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.) (Opening Brief). NRDC's Opening Brief was filed in litigation challenging EPA's Nov. 6, 2014 denial of NRDC's 2009 petition to cancel all TCVP pet products; the denial was based on the 2014 residential pet product assessment. The agency provided a point-by-point response to the NRDC's arguments in a Dec. 21, 2015 memorandum,[28] issued in conjunction with the Dec. 21, 2015 Draft TCVP Risk Assessment for Registration Review. Among the arguments presented by NRDC was that the agency "failed to consider the Davis study for the estimation of post-application risks for exposures to the TCVP pet collar." In its 2015 memorandum, the agency acknowledged consideration of the potential effect of using the Davis study as the basis for residential post-application assessment of exposures from TCVP pet collars, the study was reviewed,[29] an OPP ethics review was conducted[30], and preliminary risk estimates were presented with use of these data. However, the formal use of the Davis study was put on hold pending review by EPA's HSRB in January 2016. The Davis study includes 1) glove residue data collected by adult volunteers petting TCVP treated dogs 2) plasma cholinesterase (ChE) measures from treated dogs 3) tee shirt samples collected from children exposed to TCVP treated dogs and 4) urinary biomonitoring for adults and children exposure to TCVP treated dogs. However, for purposes of the TCVP risk assessment, EPA may rely only on the transferable residue data [in light of 40 CFR Part 26, subpart Q regarding ethical standards for assessing whether to rely on the results in human research in EPA actions] as these are the only data from the study that result in the potential for greater risks, are applicable to human exposures (in the case of the dog plasma ChE measures), or in the case of the urinary biomonitoring data, are useful given current scientific limitations (i.e., a physiologically based pharmacokinetic (PBPK) model applicable to TCVP). While EPA proposed to rely only on the

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[28] W. Britton. Tetrachlorvinphos (TCVP): Responses to Arguments Presented in the Natural Resources Defense Council, Inc.'s (NRDC) Aug. 5, 2015 Opening Brief in *NRDC v. EPA*, Case No. 15-70025 (9th Cir.). 12/21/15, D430589.

[29] W. Britton. Science Review of "Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos" for HSRB Consideration. D430707. 12/16/2015.

glove residue data (which did not involve children), since these data were collected as part of broader research which did involve children, HSRB review was necessary.

On January 12-13, 2016, the EPA HSRB addressed the scientific and ethical charge questions related to Davis study. Ethics and science reviews were conducted by the agency in support of the HSRB meeting.[30,31] A Federal Register (FR) notice was published on 4/11/2016 (69 FR 21335) and provides the following information: EPA's proposal to rely on the Davis study; the reason for review by HSRB; the background on ethical conduct of research; summary of discussion on ethics-related questions; the standards applicable to ethical conduct and reliance on data; and the availability of HSRB meeting materials.[32]

The HSRB concluded that, "The research is scientifically sound and, if used appropriately, the pet fur transferable residue data from the rubbing protocol used in the study can provide useful information for evaluating potential exposures of adults and children from contact with dogs treated with tetrachlorvinphos containing pet collars."[33] Per EPA's response to NRDC's Opening Brief arguments, "EPA would rely on these data (Davis study) for regulatory decision making if HSRB determines that the study is scientifically valid and it meets appropriate human ethics requirements," since these data result in greater potential risks than those estimated using the amitraz pet collar residue transfer study (which had been relied upon in the previous risk assessments). Accordingly, post-application risks have been assessed with use of the Davis study data only and are presented herein.

The use of the Davis study as the primary data source is consistent with, and supported by, the recommendations from the comments following the 2015 draft ORE assessment for Registration Review including those submitted by NRDC and the Hartz Mountain Corporation. Per NRDC, "the Davis Study has met the appropriate scientific and ethical criteria and should be relied upon for the evaluation of exposures from TCVP containing flea collars," and the Hartz Mountain Corporation describes that, "the glove residue data measured in the Davis et al. (2008) study are valuable because they represent actual measurements of TCVP transfer from dogs wearing commercial collars to the hands of individuals petting them." Further, NRDC states that, "EPA's utilization of transferable residue data from the amitraz study is not supported by the evidence and should not be relied upon to evaluate risk."

A summary of the Davis study and a description of how these data have been used for risk quantitation is detailed in Section 5.2 of the corresponding ORE memo (D436833).

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[30] M. Lydon. Ethics Review of Davis et al Research on Flea Collars with TCVP. 12/15/2015.

[31] W. Britton. Science Review of "Davis et al., 2008. Assessing Intermittent Pesticide Exposure from Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos" for HSRB Consideration. D430707. 12/16/2015.

[32] https://www.federalregister.gov/documents/2016/04/11/2016-08281/tetrachlorvinphos-tcvp-epa-proposal-to-rely-on-data-from-human-research-on-tcvp-exposure-from-flea

[33] Letter from Liza Dawson, PhD, Chair of the EPA HSRB to Thomas Burke, PhD, MPH, EPA Science Advisor. Subject: January 12-13, 2016 EPA Human Studies Review Board Meeting Report. March 30, 2016.

Residential Non-Cancer Post-application Exposure and Risk Equations

The algorithms used to estimate non-cancer exposure and dose for residential post-application can be found in Appendix B of D436833 and the 2012 Residential SOPs.

Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates

*Pet Collars:* As noted above, the post-application assessments for the TCVP pet collars were performed assuming pet collars could be either liquid or solid (dust) formulations, and assuming a varying liquid/dust exposure potential. All child 1 to <2 years old incidental oral exposures to pets treated with pet collars, regardless of the ratio of liquid/dust assumed, are estimated to be of concern (i.e., MOEs < 1000). When assuming a 1/99 liquid/dust formulation ratio, MOEs range from 0.91 to 7.4. When assuming a 50/50 liquid/dust formulation, MOEs range from 1.8 to 15, and when assuming a 99/1 liquid/dust formulation, MOEs range from 65 to 530. A summary of residential post-application exposures and risks from TCVP pet products is presented in Appendix I.

*Dust/Powder and Pump/Trigger Spray*: Residential post-application steady state non-cancer child 1 to < 2 years old incidental oral (hand-to-mouth) exposures to pets treated with TCVP dust/powders are estimated to be of concern (i.e., MOEs < 1000; MOE range from 98 to 640). However, child 1 to < 2 years old incidental oral exposures to pets treated with TCVP pump/trigger spray products are estimated not to be of concern (i.e., MOEs are > 1,000; MOE range from 1,600 to 15,000).

Residential Cancer Post-Application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential cancer post-application risk assessment. All exposure data and assumptions that underlie the residential post-application cancer risk estimates can be referenced in the 2014 residential assessment. Note: For purpose of quantification of estimated TCVP post-application cancer risks, HED used average percent residue transfer data for all days sampled from chemical-specific exposure data for all pet formulations assessed (i.e., the TCVP powder and pump spray study and the Davis study).

Residential Cancer Post-application Exposure and Risk Estimate Equations

As was done for residential handlers, cancer post-application risk estimates for adults were calculated using a linear low-dose extrapolation approach in which a LADD is first calculated and then compared with a $Q_1$* that has been calculated for TCVP based on dose response data in the appropriate toxicology study ($Q_1$* = 1.83 x $10^{-3}$ $(mg/kg/day)^{-1}$). The algorithms used to estimate the LADD and cancer risk for residential post-application exposure can be found in Appendix B of D436833.

It should be noted that in the past, cancer risk assessments have assumed that children are no more sensitive than adults to carcinogens (i.e., no adjustment was made to children's exposure estimates in calculating a cumulative lifetime exposure). More recently, the agency's

"Guidelines for Carcinogen Risk Assessment" (USEPA, 2005) and "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens" (USEPA, 2005) proposed age-dependent adjustment factors to be applied to children's exposure. These age-dependent factors are applied only to carcinogens shown to have a mutagenic mode of action. In general, most carcinogenic pesticides have not been shown to act through a mutagenic mode of action, and thus separate assessment of children and adults is not warranted. Any pesticide found to be a carcinogen acting through a mutagenic mode of action should be dealt with on a case by case basis, and such an assessment should follow the agency's 2005 guidance. Once the results of the newly-required mutagenicity studies have been submitted and reviewed, the need for an updated cancer assessment will be determined.

Summary of Residential Post-application Cancer Exposure and Risk Estimates

*Pet Collars:* Residential cancer (adult only) risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio range from $10^{-5}$ to $10^{-4}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1 liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$.

*Dust/Powder and Pump/Trigger Spray:* Residential cancer (adult only) risks estimated for TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$.

Adult residential post-application dermal cancer risk estimates are presented in Appendix J.

## 6.3 Spray Drift

A quantitative spray drift assessment was not conducted because the use of TCVP for direct animal treatment to livestock and their premises, in kennels, outdoors as a perimeter treatment, and as a flea treatment on cats and dogs are either 1) not applied via aircraft, groundboom, or airblast equipment or 2) for applications to poultry buildings with groundboom equipment, the use is indoors and not anticipated to be a significant source of spray drift.

## 6.4 Residential Bystander Post-Application Inhalation Exposure

A quantitative residential post-application inhalation exposure assessment was not performed, as inhalation exposure is expected to be negligible from applications to pets.

# 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, for food use pesticides, aggregate risk assessment must consider exposures from three sources: food, drinking water, and residential uses. These exposures could occur from three major routes: oral, dermal, and inhalation. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating



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exposures and risks from various sources, HED considers both the route and duration of exposure.

## 7.1 Acute Aggregate Risk

The acute aggregate risk assessment combines exposures to TCVP from food and drinking water. While drinking water exposures alone were not of concern, there are acute risk estimates of concern for food only; therefore, a quantitative acute aggregate risk assessment was not conducted.

## 7.2 Steady State Aggregate Risk

The steady state aggregate assessment includes the steady state dietary (food and water) and residential exposures. However, because there are risks of concern associated with both dietary (food) and residential exposure, a quantitative steady state aggregate risk assessment was not conducted.

## 7.3 Cancer Aggregate Risk

The cancer aggregate risk assessment combines residential and dietary (food and drinking water) expected lifetime exposures for adults. For TCVP, a cancer aggregate assessment was performed for adult handlers and for adult post-application activities related to residential pet product use.

The residential handler cancer aggregate assessment uses exposures from applying TCVP products to pets (collars, dust/powders, and pump/trigger sprays). Residential handler cancer (dermal) risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio are all $10^{-7}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates are all $10^{-7}$. When assuming a 99/1 liquid/dust formulation for pet collars, the residential handler cancer risk estimates are all $10^{-8}$. Residential handler estimated cancer risks (combined dermal and inhalation) for TCVP dusts/powders range from $10^{-9}$ to $10^{-7}$, and for pump/trigger sprays range from $10^{-9}$ to $10^{-8}$. The cancer dietary (food and drinking water) assessment resulted in an estimated risk of $9 \times 10^{-7}$. The cancer aggregate assessment combines the highest (worst case) handler exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type.

The cancer aggregate (dietary and residential exposures) risk estimates for handlers are in the $10^{-7}$ to $10^{-6}$ range and are presented in Table 7.3.1.

The residential post-application cancer aggregate assessment uses dermal exposures from contacting pets treated with TCVP products (collars, dust/powders, and pump/trigger sprays). Residential cancer post-application risk estimates for TCVP pet collars assuming a 1/99 liquid/dust formulation ratio range from $10^{-5}$ to $10^{-4}$. When assuming a 50/50 liquid/dust formulation ratio, cancer risk estimates range from $10^{-5}$ to $10^{-4}$. When assuming a 99/1



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liquid/dust formulation ratio, cancer risk estimates range from $10^{-6}$ to $10^{-5}$. Post-application cancer risks estimated for handlers of the TCVP dust/powder products range from $10^{-7}$ to $10^{-6}$, and for TCVP pump/trigger sprays are all $10^{-7}$. The cancer aggregate assessment combines the highest (worst case) post-application exposure for each pet product formulation type with dietary exposure; this results in aggregate cancer risk estimates that are protective of exposures to other registered pet products of the same formulation type.

The cancer aggregate (dietary and residential exposures) post-application risk estimates are in the $10^{-6}$ to $10^{-4}$ range and are presented in Table 7.3.2.

**Table 7.3.1. Adult Handler Aggregate Cancer Risk Estimates for TCVP Pet Products**
***(Risk is estimated using a Q* of 0.00183)***

| Product Formulation Type | Reg No.; Animal type; Animal size | Food and Water Exposure (mg/kg/day)[1] | Residential Exposure (LADD, mg/kg/day)[2] | Aggregate Cancer Risk (food, water, residential) |
|---|---|---|---|---|
| **Pet Collar** (1/99 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $1.1 \times 10^{-4}$ | $1 \times 10^{-6}$ |
| **Pet Collar** (50/50 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $5.9 \times 10^{-5}$ | $1 \times 10^{-6}$ |
| **Pet Collar** (99/1 liquid/dust assumption) | 2596-139: Cat; Any | $5.1 \times 10^{-4}$ | $8.5 \times 10^{-6}$ | $9 \times 10^{-7}$ |
| **Dust/Powder** | 67517-82: Dog; Large | $5.1 \times 10^{-4}$ | $2.3 \times 10^{-4}$ | $1 \times 10^{-6}$ |
| **Pump/Trigger Spray** | 2596-125, -140: Dog (Trigger); Large | $5.1 \times 10^{-4}$ | $3.9 \times 10^{-5}$ | $1 \times 10^{-6}$ |

[1] Table 5.4.5.1
[2] Appendix D of ORE Memo D436833.
[3]Aggregate Cancer Risk = ($Q_1$*) (Food & Water Exposure + Residential LADD)

**Table 7.3.2. Adult Post-Application Aggregate Cancer Risk Estimates for TCVP Pet Products**
***(Risk is estimated using a Q* of 0.00183)***

| Product Formulation Type | Reg No.; Animal type; Animal size | Food and Water Exposure (mg/kg/day)[1] | Residential Exposure (LADD, mg/kg/day)[2] | Aggregate Cancer Risk (food, water, residential) |
|---|---|---|---|---|
| **Pet Collar** (1/99 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $3.4 \times 10^{-1}$ | $6 \times 10^{-4}$ |

| Table 7.3.2. Adult Post-Application Aggregate Cancer Risk Estimates for TCVP Pet Products *(Risk is estimated using a Q* of 0.00183)* | | | | |
|---|---|---|---|---|
| **Product Formulation Type** | **Reg No.; Animal type; Animal size** | **Food and Water Exposure (mg/kg/day)[1]** | **Residential Exposure (LADD, mg/kg/day)[2]** | **Aggregate Cancer Risk (food, water, residential)** |
| **Pet Collar** (50/50 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $1.8 \times 10^{-1}$ | $3 \times 10^{-4}$ |
| **Pet Collar** (99/1 liquid/dust assumption) | 2596-139: Dog; Small | $5.1 \times 10^{-4}$ | $1.6 \times 10^{-2}$ | $3 \times 10^{-5}$ |
| **Dust/Powder** | 2596-78: Cat; Small | $5.1 \times 10^{-4}$ | $1.9 \times 10^{-3}$ | $2 \times 10^{-6}$ |
| **Pump/Trigger Spray** | 2596-126, 140: Cat (Trigger); Small | $5.1 \times 10^{-4}$ | $5.3 \times 10^{-4}$ | $2 \times 10^{-6}$ |

[1] Table 5.4.5.1
[2] Appendix F of ORE Memo D436833.
[3]Aggregate Cancer Risk = ($Q_1$*) (Food & Water Exposure + Residential LADD)

## 8.0 Occupational Exposure/Risk Characterization

Occupational and Residential Exposure Memo: D436833, 12/21/2016, W. Britton.

Occupational handler risks have been updated herein to reflect changes in the policy used for inhalation assessment since the 2015 ORE assessment. Previously, HED was using multiple human equivalent doses (HEDs) specific to different handler activities. The current policy recommends that only a single HED is necessary to assess all potential occupational handler activities. All other occupational handler data, assumptions, and algorithms used for the 2015 ORE assessment remain the same.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects.

### 8.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

***Mixer/Loaders:***

(1a) Liquid: Groundboom Applications
(1b) Liquid: Paint Applications
(2a) Wettable Powder: Groundboom Applications
(2b) Wettable Powder: Paint Applications
(3a) Dust: Paint Applications

***Applicators:***

(4) Groundboom Applications
(5) Open Pour Liquid Additive for Feed Through
(6a) RTU Pet Collar – 1/99 Liquid/Dust Formulation
(6b) RTU Pet Collar – 50/50 Liquid/Dust Formulation
(6c) RTU Pet Collar – 99/1 Liquid/Dust Ratio Formulation
(7) RTU Dust/Powder – Pets
(8) RTU Pump/Trigger Sprays - Pets

***Mixer/Loader/Applicators:***

(9a) Liquid: Backpack Sprayer
(9b) Liquid: Manually-Pressurized Handwand
(9c) Liquid: Mechanically-Pressurized Handgun
(9d) Liquid: Backrubber or Facerubber
(10a) Wettable Powder: Backpack Sprayer
(10b) Wettable Powder: Manually-Pressurized Handwand
(10c) Wettable Powder: Mechanically-Pressurized Handgun
(10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary)
(10e) Wettable Powder: Rotary Duster
(10f) Wettable Powder: Plunger Duster
(11a) Dust: Self-Treating Dust Bag
(11b) Dust: Shaker Can
(11c) Dust: Rotary Duster
(11d) Dust: Plunger Duster
(12a) Paint: Brush or Roller
(12b) Paint: Airless Sprayer
(13) Solid Feed Additive for Feed Through: Cup

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis. Application rate: A summary of all TCVP occupational use sites and application rates is presented in Appendix A of D436833.

*Pet Collar Formulation Assumptions:* As was mentioned in the residential sections, due to the uncertainty associated with whether TCVP pet collars are liquid and/or dust formulated products, handler steady state inhalation exposures for TCVP pet collar application were assessed assuming pet collars could be liquid and solid (dust) formulations concurrently with varying ratios of liquid/dust. The liquid formulation UE data assumes negligible inhalation exposure; therefore, only the dust-specific UE data is expected to result in the potential for inhalation exposures. In the case of handlers, therefore, the dust formulation drives any potential exposure.

*Unit Exposures:* It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[34]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the agency website[35].

A single chemical-specific exposure study, Monitoring Exposure of Mixer/Loaders and Applicators Treating Agricultural Premises with Tetrachlorvinphos (Rabon® 50 WP Insecticide) in Handheld Wand-Type Sprayers (MRID 42622301), was used as appropriate (i.e., exposure scenario 10c, mix/load and apply WP with mechanically-pressurized handgun) in the most recent occupational risk assessment for TCVP.[36] Per the prior risk assessment, risks for the exposure scenario were estimated with use of the chemical-specific exposure data as well as surrogate PHED data. This exposure study was summarized in the 2015 draft ORE assessment Registration Review[37].

The PHED data recommended for the exposure scenario reflects unit exposure values (dermal and inhalation) that represent an individual conducting all activities, mixing/loading/applying, for use of the WP product by mechanically pressurized handgun. In contrast, the chemical-specific exposure study was conducted in a manner which separated out the mixing/loading and application components of the exposure scenario. Exposure scenario 10c has been assessed, and estimated risks presented separately, (i.e., mixer/loader and applicator) with use of the chemical-specific data, and for all activities with use of PHED. When applied, the dermal and inhalation unit exposures resulting for product application result in risk estimates that are very similar to risk estimates using the PHED data. Non-cancer and cancer private/farmer and

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[34] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[35] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html
[36] J. Dawson. Tetrachlorvinphos: Further Revisions to Occupational Risk Assessment for Uses in the Poultry and Cattle Production Industries. 3/28/2002. D281972.
[37] W. Britton. Tetrachlorvinphos: Occupational and Residential Exposure Assessment for Registration Review. 12/21/2015. D426984.

contract/commercial occupational handler risk estimates for exposure scenario 10c are presented separately from the risk summaries for all other occupational handler exposure scenarios in Appendix K: Table K.2 and Appendix L: Tables L.2 and L.4, respectively.

In some cases, due to the lack of data for an exposure scenario or the unique nature of the scenario, surrogate exposure data were used as follows:

- Exposure data for the loading/application of dust formulations were used as a surrogate for the loading/application of wettable powders for rotary and plunger duster applications (10e, 10f). For exposure scenario 10e, exposure data for plunger dusters were used due to the lack of data for the rotary duster application method.
- For the assessment of pet collars as a dust formulation, data for applying dusts using a shaker can were used as a surrogate.
- Unlike more typical exposure scenarios where a RTU paint is only loaded or applied, for TCVP the paint must be mixed/loaded for the liquid (1b), wettable powder (2b), and dust (3a) formulations. These exposure scenarios were assessed using the exposure data appropriate for mixing/loading for each formulation with the exception of dust where WP formulation was used as a surrogate for dust.
- For TCVP applications to livestock with a dust formulation via shaker can, a RTU product is not available; therefore, exposures from the mixing/loading of the dust formulation must be assessed in addition to potential exposure resulting from application via shaker can. As a result, the exposure data for the loading/application via a RTU shaker can was used for the assessment of all scenarios relating to the use. The use of these data results in a more protective assessment than would be if the mixing/loading of the dust were assessed separately.
- Exposures from the application of feed (salt or mineral) blocks in livestock – typically, 5 – 15 per head of cattle or horses – is assumed to be negligible if gloves are worn when placing the blocks. Furthermore, for these products the greater majority of the active ingredient is contained within the block, thus further reducing the exposure potential.

*Area Treated or Amount Handled:* The following inputs are consistent with those used in the most recently conducted occupational risk assessment for TCVP and, for those inputs relating to the poultry industry, are reflective of research conducted by BEAD at that time.

- Groundboom: 100,000 square feet for applications to poultry buildings
- Backpack and manually pressurized handwand: 20,000 square feet for applications to poultry buildings
- Mechanically pressurized handwand: 100,000 square feet for applications to poultry buildings
- Backpack, handheld/stationary fogger, manually pressurized handwand, mechanically pressurized handwand, rotary spreader: 20,000 birds for direct application to poultry (i.e., approximately 1 square foot/bird)
- Backrubber/facerubber: 50 gallons
- Paint applications: 2 gallons



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The following inputs are based on either the most recently conducted permethrin occupational and residential exposure and risk assessment for similar use patterns[38] or best professional judgment of product usage:

- All handheld equipment: 400 animals treated daily
- Handheld/stationary fogger: 100,000 square feet to poultry buildings
- Plunger, shaker can, spoon: 1,000 birds or 1,000 square feet
- Pet collar, pump/trigger spray, and shaker can applications: 8 animals treated daily
- Self-treating dust bags: 10 filled daily (assuming a 12.5 lb dust bag)

The following inputs are consistent with EPA regulatory definitions for large concentrated animal feeding operations (CAFOs)[39]. The inputs assume that a single individual is responsible for the food preparation for the entire CAFO and applies the TCVP feed-through products to the animal feed.

- Cup, pour on: 1,000 cows, 500 horses, and 6,250 pigs for liquid and solid feed-through applications. The number of cows and horses represents the maximum identified for large CAFO operations. The number of pigs was estimated by averaging the maximum number weighing over 55 lbs (2,500) and less than 55 lbs (10,000) in large CAFO operations.

*Exposure Duration*: Occupational handler exposure is expected to be short- and intermediate-term in duration. Because of the steady state AChE inhibition exhibited by the OPs, steady state exposures (typically 21 days and longer for OPs, but 1 day to reach steady state for tetrachlorvinphos) were assessed and presented for occupational exposures to TCVP products.

*Mitigation/Personal Protective Equipment:* Estimates of non-cancer inhalation exposure were calculated for various levels of PPE (i.e., respiratory protection). Results are presented for no respirator, PF5 respirator, PF10 respirator, or engineering controls (EC).

The PPE required for occupational use of TCVP varies by formulation type. The respiratory protection required for the occupational handling of TCVP can, at times, differ from label to label with consideration of the same formulation and exposure scenario. Occupational handler exposures are expected from use of TCVP on livestock and pets by livestock handlers, veterinarians, veterinary assistants, and groomers. The pet use formulations include collars, dusts/powders, and pump and trigger sprays. All but one of the TCVP pet product labels do not require PPE, as these are intended for residential sale as well as for occupational use. A summary of PPE required for all TCVP products is presented in Appendix A of D436833.

*Days per Year of Exposure:* To assess cancer risk, it is assumed that private/farmers would be exposed 10 days per year and commercial applicators would be exposed 30 days per year. The

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[38] C. Smith. Permethrin: Third Revision of the Occupational and Residential Exposure Assessment for the Reregistration Eligibility Decision Document. 4/4/2006. D325428.
[39] http://www.epa.gov/npdes/pubs/sector_table.pdf

term "private/farmer" means that the applicators or one of the workers would apply the pesticides to land owned or operated by the farmer. Commercial applicators mean the applicators are completing multiple applications for multiple clients.

*Years per Lifetime of Exposure:* It is assumed that handlers would be exposed for 35 years out of a 78-year lifespan.

*Lifetime Expectancy:* Life expectancy values are from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males was 75 years and 80 years for females. Based on the available data, the recommended value for use in cancer risk assessments is 78 years.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix B of D436833.

Combining Exposures/Risk Estimates

Although occupational dermal and inhalation exposures are anticipated for TCVP, risks have been estimated for inhalation exposures only due to the lack of dermal hazard. Therefore, no combined occupational exposures/risk estimates have been quantified.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Of the 198 total occupational handler exposure scenarios assessed, the majority (162) are not of concern (i.e., steady state inhalation MOEs are $\geq$ 300) with currently required personal protective equipment (PPE) (i.e., respiratory protection). Of the remaining 36 handler exposure scenarios, 25 are not of concern with consideration of increasing levels of respiratory protection (i.e., 11 occupational handler exposure scenarios result in estimated risks of concern despite the addition of respiratory protection or engineering controls; MOEs at highest level of respiratory protection range from 3.9 to 280). These eleven handler scenarios include dust formulations (mixing/loading/applying TCVP by rotary duster, self-treating dust bag, or shaker can) and wettable powder formulations (mixing/loading/applying TCVP by mechanically-pressurized handgun using MRID 42622301 and mixing/loading/applying using fogging equipment).

A summary of all non-cancer occupational handler exposure scenarios is presented in Appendix K. For risk management purposes, the currently labeled level of respiratory protection and EC has been identified (shaded) for each individual exposure scenario.

Occupational Handler Cancer Exposure and Risk Equations

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which an LADD is first calculated and then compared with a Q1* that has been calculated for TCVP based on dose response data in the appropriate toxicology study (Q1* = $1.83 \times 10^{-3}$ (mg/kg/day)-1). ADD levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the Q1* to obtain cancer risk estimates. The algorithms used to

estimate the LADD and cancer risk for occupational handlers can be found in Appendix B of D436833.

Summary of Occupational Handler Cancer Exposure and Risk Estimates
Occupational cancer risks were estimated for both private/farmer and contract/commercial handlers. Cancer risks, with currently required PPE, range from $10^{-10}$ to $10^{-5}$ for private/farmer handlers and from $10^{-10}$ to $10^{-4}$ for contract/commercial handlers with currently required PPE.

Unlike the occupational handler non-cancer risk estimates which were based only on inhalation exposures, the occupational handler cancer risk estimates are quantified based on both dermal and inhalation exposures. This is because, despite the determination of the lack of dermal hazard for TCVP, dermal exposures from TCVP must be quantified for the purpose of cancer risk assessment. As previously described, the PPE required for the occupational use of TCVP varies by formulation type. For example, for feed through (solid and liquid food additives) and feed blocks, occupational handlers are required to wear baseline clothing (i.e., long sleeved shirt, long pants, shoes and socks) and gloves. For all other end-use labels with livestock and outdoor perimeter uses, required PPE can vary dependent on the application type or equipment and can range from baseline clothing and gloves, to the addition of coveralls, or respiratory protection.

A summary of occupational cancer risks as estimated at all levels of personal protection and with use of engineering controls is presented in Appendix L. Tables L.1 and L.2 present cancer risks for private/farmer handlers and Tables L.3 and L.4 risks for contract/commercial handlers. For risk management purposes, the currently labeled level of respiratory protection and EC has been identified (shaded) for each individual exposure scenario.

## 8.2 Occupational Post-application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties.

Occupational post-application exposures are not anticipated for TCVP as the majority of application scenarios are not to foliar surfaces. The use of TCVP outdoors as a perimeter treatment is not expected to result in occupational post-application exposure as reentry activities related to crop production (e.g., scouting, harvesting) are not anticipated for this use pattern.

## 9.0 Public Health and Pesticide Epidemiology Data

Incident Report Memo: D426986, 5/21/15, S. Recore [40]

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[40] S. Recore *et al.*, 5/21/2015, D426986, Tetrachlorvinphos (TCVP): Tier I Review of Human Incidents for Draft Risk Assessment

HED has prepared a Tier I review of human incidents report. For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient TCVP. The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to TCVP exposure.

The Agricultural Health Study (AHS) is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer. TCVP is not included in the AHS, and therefore this study does not provide information for this report.

Although there were a moderate number of TCVP incidents reported to Main and Aggregate IDS (n=374) and SENSOR-Pesticides (n=61), most of these incidents were classified as low severity. The effects experienced were generally minimally traumatic and resolving rapidly and usually involve skin, eye or respiratory irritation. Most of the reported incidents were due to handling and applying TCVP products to pets. Based on the low severity of incident cases reported for TCVP in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. The agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

## 10.0 Cumulative Exposure/Risk Characterization

OPs, like TCVP, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PoDs for each OP, including TCVP. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.5, OPP has retained the FQPA Safety Factor for OPs, including TCVP, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes.

The agency will continue to evaluate the epidemiology studies associated with neurodevelopmental outcomes and OP exposure prior to release of the revised risk assessment. During this period, the agency will determine whether or not it is appropriate to apply the draft guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis for the neurodevelopment outcomes.

## 11.0 Appendices

Appendix A. Toxicology Profile
Appendix B. Results for BMD/BMDL modeling for TCVP
Appendix C. Methodologies for HEC Calculations
Appendix D. Physical/Chemical Properties for Tetrachlorvinphos
Appendix E. TCVP and Metabolites
Appendix F. International MRLs and U.S. Tolerances
Appendix G. Summary of Residential Handler Non-Cancer Exposures and Risk Estimates
Appendix H. Summary of Residential Handler Cancer Exposure and Risk Estimates
Appendix I. Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates
Appendix J. Summary of Residential Post-Application Cancer Exposure and Risk Estimates
Appendix K. Summary of Occupational Handler Non-Cancer Exposures and Risk Estimates
Appendix L. Summary of Occupational Handler Cancer Exposures and Risk Estimates



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## Appendix A. Toxicology Profile and Executive Summaries

### A.1. Toxicology Data Requirements

The requirements (40 CFR 158.500) for the food use for TCVP are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

| Study | Technical | |
|---|---|---|
| | Required | Satisfied |
| 870.1100 Acute Oral Toxicity | yes | yes |
| 870.1200 Acute Dermal Toxicity | yes | yes |
| 870.1300 Acute Inhalation Toxicity | yes | yes |
| 870.2400 Primary Eye Irritation | yes | yes |
| 870.2500 Primary Dermal Irritation | yes | yes |
| 870.2600 Dermal Sensitization | yes | yes |
| 870.3100 90-Day Oral Toxicity in Rodents | yes | yes |
| 870.3150 90-Day Oral Toxicity in Non-rodents | yes | yes [a] |
| 870.3200 21/28-Day Dermal | yes | yes |
| 870.3250 90-Day Dermal | no | - |
| 870.3465 90-Day Inhalation | yes | yes [b] |
| 870.3700a Prenatal Developmental Toxicity in Rodents | yes | yes |
| 870.3700b Prenatal Developmental Toxicity in Non-rodents | yes | yes |
| 870.3800 Reproduction | yes | yes |
| 870.4100a Chronic Toxicity in Rodents | yes | yes |
| 870.4100b Chronic Toxicity in Non-rodents | yes | yes |
| 870.4200a Carcinogenicity in Rats | yes | yes |
| 870.4200b Carcinogenicity in Mice | yes | yes |
| 870.4300 Chronic Toxicity/Carcinogenicity in Rats | yes | yes |
| 870.5100 Mutagenicity—Bacterial Reverse Mutation Test | yes | yes |
| 870.5300 Mutagenicity—Mammalian Cell Gene Mutation Test | yes | yes |
| 870.5375 Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.5xxx Mutagenicity—Other Genotoxic Effects | yes | no[c] |
| 870.6100a Acute Delayed Neurotoxicity in Hens | yes | yes |
| 870.6100b 90-Day Neurotoxicity in Hens | yes | yes |
| 870.6200a Acute Neurotoxicity Screening Battery in Rats | yes | yes |
| 870.6200b 90-Day Neurotoxicity Screening Battery in Rats | yes | yes |
| 870.6300 Develop. Neurotoxicity | yes | yes |
| 870.7485 General Metabolism | yes | yes |
| 870.7600 Dermal Penetration | yes | yes |
| 870.7800 Immunotoxicity | yes | yes |
| Special Studies<br>Comparative Cholinesterase in Rats | yes | yes |

[a] there is a chronic study; [b] 4-Week study

[c] A follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) and a study that investigates possible genotoxic activity in the target organ (liver) are required. This latter study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target).



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## A.2 Toxicity Profiles

| Table A.2.1 Acute Toxicity of Tetrachlorvinphos Technical | | | | |
|---|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No.** | **Results** | **Toxicity Category** |
| 870.1100 | Acute Oral – Rat | 41222504 | $LD_{50}$ =<br>1480 mg/kg (M)<br>465-965 mg/kg (F) | III |
| 870.1200 | Acute Dermal – Rabbit | 41222505 | $LD_{50}$ > 2000 mg/kg | III |
| 870.1300 | Acute Inhalation – Rat | 00138933 | LC50 > 3.61mg/L | IV |
| 870.2400 | Acute Eye Irritation - Rabbit | 41222506 | moderate | III |
| 870.2500 | Acute Dermal Irritation - Rabbit | 41222507 | slight | IV |
| 870.2600 | Skin Sensitization - Guinea Pig | 41377902<br>42981001 | sensitizer | N/A |
| 870.6100 | Acute Delayed Neurotoxicity | 41905901 | No clinical signs of neurotoxicity observed (NTE not measured) | N/A |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3100<br>21-Day Oral Toxicity in (Crl:CD®(SD)IGS BR rats) | 45570601<br>(2001)<br>Acceptable/non-guideline (21-day study; gavage)<br>0, 8, 12, 20, or 50 mg/kg/day | **Repeat exposure**:<br>Brain ChEI NOAEL = 12 mg/kg/day<br>Brain ChEI LOAEL = 20 mg/kg/day, based on brain cholinesterase activity inhibition in females (day 21).<br><br>RBC ChEI NOAEL = 8 mg/kg/day<br>RBC ChEI LOAEL = 12 mg/kg/day, based on RBC cholinesterase activity inhibition in males and females<br>***HIARC: RBC data not reliable***<br>**Single dose exposure**:<br>RBC ChEI NOAEL = 20 mg/kg.<br>RBC ChEI LOAEL = 50 mg/kg, based on RBC cholinesterase activity in both sexes.<br>NOTE: *HIARC: RBC data not reliable from this study.*<br><br>Brain ChEI NOAEL =12 mg/kg.<br>Brain ChEI LOAEL = 20 mg/kg, based on brain cholinesterase activity inhibition (ChEI) in males (22%). At 50 mg/kg, males had 54% and females had 23% brain cholinesterase inhibition.<br><br>$BMDL_{10}$ = 6.7 mg/kg/day<br>$BMD_{10}$ = 9.9 mg/kg/day, based on female RBC ChE inhibition<br>$BMDL_{10}$ = 12.2 mg/kg/day<br>$BMD_{10}$ = 14.7 mg/kg/day, based on female brain ChE inhibition |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3150<br>90-Day Oral Toxicity<br>(Sprague Dawley rats) | 43371201 (1990)<br>Acceptable/guide line<br>0, 100, 2000, or 5000 ppm (diet)<br>Males: 0, 6.7, 142, and 375 mg/kg/day;<br>Females: 0, 10.0, 197, and 467 mg/kg/day.<br><br>$BMDL_{10}$ = 8.0 mg/kg/day<br>$BMD_{10}$ = 10.49 mg/kg/day, based on female RBC ChE inhibition | RBC ChEI NOAEL = 6.7 mg/kg/day<br>RBC ChEI LOAEL = 142 mg/kg/day, based on RBC ChEI in both sexes (males 30%*; females 79%**), bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females and mid-dose males, higher adjusted liver weights (both sexes), higher adjusted adrenal weights in females, and thyroid follicular cell hypertrophy in both sexes. At 467 mg/kg/day, in addition to RBC ChEI in both sexes (males 72%*; females 91%**), females had a 24% brain cholinesterase inhibition, although statistical significance was not attained (females 12%, 14%, 24% brain ChEI with increasing dose; males 1% at HDT). Additionally, decreased body weight was observed throughout the study in males (7%- 12%), with the magnitude of the deficit increasing over time.<br><br>$BMDL_{10}$ = 8.0 mg/kg/day<br>$BMD_{10}$ = 10.49 mg/kg/day, based on female RBC ChE inhibition<br>$BMDL_{10}$ = 26.3 mg/kg/day<br>$BMD_{10}$ = 61.6 mg/kg/day, based on male RBC ChE inhibition<br>No dose-response for brain ChE inhibition (BMD not run) |
| 870.3200<br>21/Day Dermal Toxicity (Crl:CD BR Sprague Dawley rat) | 41342001 (1989)<br>Acceptable/guide line<br>0, 10, 100, or 1000 mg/kg/day<br>6 hours/day, 5 days/week for 15 treatments over a 21-day period | NOAEL = 1000 mg/kg/day<br>LOAEL = not determined.<br>RBC and brain cholinesterase inhibition were not observed in either sex at dose levels up to and including the limit dose.<br><br>Significant dermal effects were not observed. There were no treatment-related effects on body weight, food consumption, hematology or clinical chemistry parameters (except plasma ChE activity), gross or microscopic pathology in either sex.<br>Plasma ChE inhibition was observed in females at 1000 mg/kg/day. |
| 870.3465<br>28-Day Inhalation Toxicity<br>(Sprague-Dawley rat) | 48803501 (2012)<br>Acceptable/guide line<br>nose-only aerosol<br>6 hours/day, 5 days/week for 3 weeks at exposure concentrations of 0, 0.05, 0.5, or 1.0 mg/L; during the final week of exposure (week 4), the animals were exposed for 7 days | NOAEL= 0.05 mg/L/day<br>LOAEL = 0.5 mg/L/day, based on an increase in RBC cholinesterase inhibition in both sexes. *Brain cholinesterase activity was not monitored.*<br><br>Systemic NOAEL not identified.<br>Systemic LOAEL = 0.05 mg/L, based on diffuse adrenal cortical cell vacuolation in both sexes, enlarged adrenals in females, and increased adrenal weights in females. At 0.5 mg/L and 1.0 mg/L, in addition to the adrenal findings, there was a dose-related increase in vacuolation of the ovaries in females, an increase in squamous metaplasia of the larynx in both sexes, and an increase in follicular cell hyperplasia of the thyroids in both sexes.<br><br>**Sex/Age** \| **Compartment** \| **$BMD_{10}$** \| **$BMDL_{10}$**<br>Female \| RBC \| 0.394 \| 0.050<br>Male \| RBC \| 0.122 \| 0.022 |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.3700a Prenatal developmental in (Sprague Dawley Crl:COBS®CD ® (SD)BR)<br><br>TXR# 008124, 008616, 018781 | 40152701 (1987)<br>41828001(1991)<br>41967201 (1991)<br>42520101 (1992)<br>Acceptable/guide line<br>0 (aqueous 0.5% methyl cellulose), 75, 150, or 300 mg/kg/day<br>GD 6-15; 10 mL/kg (gavage) | **Maternal** NOAEL = 75 mg/kg/day<br>**Maternal** LOAEL = 150 mg/kg/day, based on a reduction in BWG/FC*<br>At 300 mg/kg/day, there were clinical signs of toxicity (tremors and chromodacryorrhea)<br>**Developmental** NOAEL =300 mg/kg/day<br>**Developmental** LOAEL = not identified.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).*<br><br>*BWG not considered an adverse effect since BW was not affected. NOAL/LOAEL should be revised to 150/300 mkd. |
| 870.3700b Prenatal developmental in (New Zealand white rabbit) | 00127831 (1982)<br>Acceptable/guide line<br>0, 150, 375, or 750 mg/kg/day (1% CMC)<br>GD 6-19; 5 mL/kg (gavage) | **Maternal** NOEL = 375 mg/kg/day<br>**Maternal** LOEL = 750 mg/kg/day, based on mortality, abortions, and red vaginal fluid.<br>**Developmental** NOAEL = 375 mg/kg/day<br>**Developmental** LOAEL = 750 mg/kg/day, based on an increase in early resorptions and corresponding increase in post implantation loss, and a decrease in live fetuses/doe.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).* |
| 870.3800 Reproduction and Fertility Effects (Charles River CD Crl®SD) BR rats) | 42054301 (1991)<br>acceptable/guidel ine<br>0, 100, 500, or 2000 ppm (diet)<br>F0 Males 0, 5.2, 26, 102 mg/kg/day<br>F1 Males 0, 6.7, 34, 130 mg/kg/day<br><br>F0 Females 0, 7.3, 40, or 155 mg/kg/day<br>F1 Females 0, 8.3, 43, or 168 mg/kg/day | **Parental** NOAEL = 500 ppm (males 26/females 40 mg/kg/day)<br>**Parental** LOAEL = 2000 ppm (males 102/females 155 mg/kg/day), based on decreased body weight gain in F1 generation, increased adrenal weights of F0 females, and decreased body weight gains in F0 males.<br>**Offspring** NOAEL = 2000 ppm (males 102/females 155 mg/kg/day)<br>**Offspring** LOAEL was not identified.<br>**Reproductive** NOAEL = 2000 ppm (males 102/females 155 mg/kg/day)<br>**Reproductive** LOAEL was not identified.<br><br>*NOTE: Cholinesterase activity was not assessed (RBC, brain).* |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4100a Chronic Toxicity (Sprague-Dawley rat) | 42980901 (1993)<br>43335101 (1994)<br>Acceptable/guideline<br>0, 100, 1000, or 2000 ppm (diet)<br>Males 0, 4.23, 43.2, or 88.5 mg/kg/day<br>Females 0, 5.93, 62.7, or 125.3 mg/kg/day<br>(2-year study) | NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes); reduced body weight; ~~plasma~~ cholinesterase inhibition in females.<br>RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **); brain ChEI in females at 52 and 104 weeks was 17% and 16% (not **).<br>NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on RBC cholinesterase inhibition in females<br><br>BMD not run due to lack of dose-response |
| 870.4100b Chronic toxicity (Beagle dog) | 42679401 (1993)<br>Acceptable/guideline<br>0, 0, 6.25, 500, 1000 mg/kg/day; (capsule)<br>4/sex/group<br>Cholinesterase pre-test, 12, 26, 52 weeks (plasma, RBC)<br>Brain at termination (1 year) | NOAEL = 6.25 mg/kg/day<br>LOAEL = 500 mg/kg/day, based on plasma cholinesterase inhibition (both sexes), decreased red blood cell counts, hemoglobin, hematocrit, MCHC, MCV, alkaline phosphatase, urine specific gravity, and decreased liver and kidney weights.<br>At 1000 mg/kg/day, increased white blood cell counts (females), increased prostate weight, decreased cholesterol (males).<br>RBC and brain cholinesterase inhibition were not observed at any dose level in either sexes. |
| 870.4200a Carcinogenicity (Sprague Dawley rat) | 42980901 (1993)<br>43335101 (1994)<br>acceptable/ guideline<br>0, 100, 1000, or 2000 ppm (diet)<br>Males 0, 4.23, 43.2, or 88.5 mg/kg/day<br>Females 0, 5.93, 62.7, or 125.3 mg/kg/day<br>104 weeks | NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes); reduced body weight; cholinesterase inhibition in females.<br>RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **); brain ChEI in females at 52 and 104 weeks was 17% and 16% (not **).<br>NOAEL = 100 ppm (4.23/5.93 mg/kg/day)<br>LOAEL = 1000 ppm (43.2/62.7 mg/kg/day), based on RBC cholinesterase inhibition in females<br>BMD not run due to lack of dose-response<br>Increased incidence of thyroid C-cell adenomas in male rats at HDT and adrenal pheochromocytomas in males |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.4200b Carcinogenicity (B6C3F1 mouse) | 00117443 (1978) Acceptable/guideline 0, 17.5, 64, 320, 1600, 8000, 16000 ppm 0, 2.6, 9.6, 48, 240, 1200, or 2400 mg/kg/day | NOAEL = 1600 ppm (240 mg/kg/day)<br>LOAEL = 8000 ppm (1200 mg/kg/day), based on decreased body weight gain<br>Statistically significant increases in combined hepatocellular adenoma/carcinoma (primarily carcinomas) in female B6C3F1 mice at 1600 ppm.<br>Other doses considered excessive; combined adenomas/carcinomas in males, renal adenomas/carcinomas and combined in males at 16000 ppm |
| 870.4300 Combined Chronic Toxicity/Carcinogenicity (Sprague Dawley rat) | 42980901 (1993) 43335101 (1994) acceptable/guideline 0, 100, 1000, or 2000 ppm Males 0, 4.23, 43.2, or 88.5 mg/kg/day Females 0, 5.93, 62.7, or 125.3 mg/kg/day | See above 870.4200a |
| 870.4200a Carcinogenicity (Osborne-Mendel rats) | 00117443 () Acceptable/non-guideline 0, 4250, or 8500 ppm for 80 weeks | Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. . High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid. Study deficiencies (CPRC, 1988); evidence equivocal. |
| Gene Mutation 870.5100 *Salmonella/Escherichia* bacterial reverse mutation assay | 41222508 (1989) Acceptable/ Guideline 66.7, 100, 333, 667, 1000, or 3300 µg/plate in the presence of or 10, 33.3, 66.7, 100, 333, or 667 µg/plate absence of mammalian metabolic activation (S9-mix) | Strains TA98, TA100, TA1535, TA1537, and TA 1538 of *S. typhimurium* were exposed to TCVP from concentrations of 66.7 to 3300 µg/plate in the presence and 10-667 µg/plate absence of mammalian metabolic activation (S9-mix).<br>There was no evidence of induced mutant colonies over background. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| *In vitro* mammalian cytogenetics 870.5375 Chinese hamster ovary cells | 41312901 (1989) Acceptable/ Guideline Concentrations of 22.9, 44.9, 59.9, 79.8, or 99.8 µg/mL without S9; 12.5, 25, 37,6, or 75.1 µg/mL in the presence of S9-mix. | Positive for inducing chromosomal aberrations at 59.9, 79.8 and 99.8 µg/mL in absence of metabolic activation, but negative at 29.9 or 44.9 µg/mL in absence of metabolic activation.<br>Negative for inducing chromosomal aberrations at 12.5, 25, 37.6, or 75.1 µg/mL in the presence of rat S9 metabolic activation. |
| Unscheduled DNA Synthesis 870.5550 in mammalian cells in culture | 42156401 (1992) Acceptable/ Guideline Doses of 5, 7.5, 10, 15, 20, 23, 25, 27, 30, 35, or 40 µg/mL of TCVP. | Concentrations of 35 and 40 µg/mL were lethal. Results were negative. |
| 870.6100 Acute and 28-Day Delayed Neurotoxicity (Domestic hen) | 41905901 (1990) Acceptable/guide line 2500 mg/kg x 2 (21 days apart) | Does not cause delayed neurotoxicity; 4/15 died. |
| 870.6200a Acute Neurotoxicity Screening Battery (Sprague-Dawley Crl:CD®BR rats) | 42912501 (1993) Acceptable/guide line 0, 65, 325, or 650 mg/kg (gavage) | NOAEL = 65 mg/kg<br>LOAEL = 325 mg/kg, based on transient neurotoxic effects in both sexes consistent with cholinesterase inhibition. No neuropathological effects.<br><br>*Cholinesterase activity was not monitored in the study.* |
| 870.6200b Subchronic Neurotoxicity Screening Battery (Crl:CD® BR rats) | 43294101 (1994) Acceptable/guide line 0, 200, 1000, or 5000 ppm (diet) (0, 100, 500, or 250 mg/kg/day; standard conversion) | NOAEL = 5000 ppm (250 mg/kg/day); HDT<br>LOAEL = not identified.<br><br>*Cholinesterase activity was not monitored in the study.* |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| 870.6300 Developmental Neurotoxicity (Crl: CD® (SD)IGS BR VAF/Plus® rats) | 46660601 (2005) acceptable/guideline 0, 10, 50, or 200 mg/kg/day GD 6 –LD 6 (gavage) 46791401 (2006) +control data | **Maternal** NOAEL = 200 mg/kg/day<br>LOAEL = not identified.<br>**Offspring** NOAEL = 50 mg/kg/day<br>LOAEL = 200 mg/kg/day, based on deceased body weight, body weight gain, several morphometric linear brain measurements in both sexes, and decreased absolute brain weight in males on PND 70<br>*Cholinesterase activity was not monitored in the study.* |
| 870.7485 Metabolism and Pharmacokinetics (Sprague-Dawley CD rat) | MRID 41988401 (1991) Acceptable/guideline 5 mg/kg [single and repeat (14 days)] and 250 mg/kg (single) | Most of radioactivity recovered in urine (46%-60%) and feces (38%-56%) within 48 hours post dose; major metabolite in urine was trichloromandelic acid (18%-26%); major metabolite in feces was trichlorophenylethanol (>13%).<br>Since the oral LD50 for female rats is lower than the male LD50, it is noteworthy that males of all groups excreted more total label as trichloromandelic acid, a more completely metabolized form of TCVP; high-dose females tended to excrete more of the label as desmethyl TCVP (with the phosphate group still attached to the remainder of the molecule), a compound that could be derived from TCVP with only a single metabolic step. |
| 870.7600 Dermal Penetration (Sprague Dawley CD rats) | MRID 42111501 (1991) MRID 41862401 (1991) Acceptable/Guideline 0, 0.01, 0.1, 1, or 5 mg/cm$^2$ for exposures of 0.5, 1, 2, 4, and 10 hours and 10 hour wash with 72 hour exposure | Absorbed dose following 0.01 mg/cm$^2$ dose is 9.57% following 10-hour exposure. |
| 870.7800 Immunotoxicity (Crl:CD-1(ICR) female mouse) | 48794701 (2012) acceptable/guideline 0, 75, 300, 1200 mg/kg/day | Systemic NOAEL = 1200 mg/kg/day,<br>Systemic LOAEL = not identified.<br>Immunotoxicity NOAEL = 1200 mg/kg/day.<br>Immunotoxicity LOAEL = not identified. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special study Comparative cholinesterase<br><br>*gestational CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus rats) | MRID 48291101 (2010) Acceptable/non-guideline<br>1% aqueous (w/v) methylcellulose<br>0, 75, 150, 300 mg/kg/day<br>GD 6-21 (gavage) | The main purpose of this study was to determine whether there is differential sensitivity between dams and fetuses with respect to cholinesterase inhibition following oral exposure to TCVP.<br>***RBC ChE***: Neither the dams nor the fetuses demonstrated RBC ChE inhibition at dose levels where RBC ChE inhibition (ChEI) would be expected. The repeat dosing study (2012, 48773401) conducted in the same laboratory in the same strain of rat clearly demonstrated RBC ChE inhibition at 50 and 200 mg/kg/day in female rats. In the gestational/fetal study, RBC results in the dams were ↓5.1%, ↓15%, and ↓3% RBC ChEI, with increasing dose. The fetal RBC data were of little value because only one or two fetal samples were available for the control, low, and high dose groups and no sample was available for the mid dose group. *There was no way to compare adult and fetal RBC ChE.*activity<br>***Brain ChE.*** Brain ChE inhibition was dose dependent in dams (↓31%, ↓44% and ↓67% with increasing dose). Fetal brain ChE values (↓20%, ↓20.9% and ↓20.8%, with increasing dose) showed no dose-response and are questionable. However, the data suggest that the fetal brain ChE is not more sensitive to inhibition by TCVP than the dams.<br>***Plasma ChE***. Plasma ChE inhibition in dams was dose dependent ↓62%, ↓71% and ↓77%, with increasing dose). Fetal plasma ChE values were ↓22%, ↓18.5% and ↓20.8%, with increasing dose. The lack of a dose response raises questions as to whether these lower values are actually inhibition. However, the data do not indicate that the fetuses are more sensitive than the dams.<br><br>***Classification:*** This *in vivo* comparative ChE study is classified as **Acceptable/non-guideline**. The inability of the laboratory to detect RBC ChE in the dams and the flat dose response curves for the brain ChE in both pups and adults confounds the interpretation of the study. However, no additional gestational CCA study is being requested at this time because there is no indication that the fetuses were more sensitive than the dams. |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special studies Comparative cholinesterase<br><br>*Acute CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain rat) | MRID 48294601 (2010) Acceptable/non-guideline<br>Single gavage dose (1% aqueous methylcellulose) young adult, PND 11, PND 21 0, 75, 150 or 300 mg/kg | The main purpose of this study was to determine whether there is differential sensitivity among the PND11, PND21 and adults with respect to cholinesterase inhibition following exposure to TCVP.<br>Overall, there is little confidence in the ChE data mainly because of the lack of clear dose and temporal responses. The number of samples in many cases was inadequate due to sample loss (no sample available, 1, 2, or 3 samples). Also, duplicate samples that did not replicate contributed to the low number of samples available for a meaningful assessment. Brain ChE assessment also appeared to be affected by the low number of samples. The results for all three enzyme sources indicated that there was inhibition at all doses but there was poor dose response with the degree of apparent inhibition at the higher doses often less that at the low dose of 75 mg/kg/day. There was also a lack of temporal concordance with high apparent inhibition at one time, a much lower degree at the following time point, and back to the higher level at the next time point. Further, there was more or similar apparent inhibition at the low dose of 75mg/kg in this acute study than there was in the repeat dosing study (2012, MRID 48773401, eleven daily doses) at 200 mg/kg/day and in the gestational study (2010, MRID 48291101, fifteen daily doses). It is noted that the repeat dosing study indicated that there was no increase in sensitivity of the pups relative to the adults with regard to ChEI by TCVP. However, in this acute study, there were several comparisons among the PND11, PND21 and adults that suggested the pups were more sensitive. Although there is little confidence in the ChEI data in this study, no additional acute CCA study is being requested at this time.<br>***Benchmark Dose (BMD) modeling.*** BMD modeling was performed but could not be done with the RBC data or for the PND11 brain data because of too few samples and/or the data would not otherwise fit the models. BMD modeling for the brain ChE data (3-hour time point) indicated that for males, the adults were slightly more sensitive than the PND 21 pups but the females were considered similar with respect to the $BMD_{10}$ and $BMDL_{10}$.<br><br>**TCVP/Study** \| **Sex/Age** \| **Compartment** \| **BMD Results** (mg/kg/day) \| **$BMD_{10}$** \| **$BMDL_{10}$**<br>MRID 48294601 Acute CCA \| Adult male \| Brain \| 6.76716 \| 5.02249<br>MRID 48294601 Acute CCA \| Adult female \| Brain \| 11.2932 \| 4.55107<br>MRID 48294601 Acute CCA \| Male pup PND 21 \| RBC \| 16.8647 \| 9.71265<br>MRID 48294601 Acute CCA \| Female pup PND 21 \| Brain \| 9.80073 \| 4.6942<br>MRID 48294601 Acute CCA \| Male pup PND 21 \| Brain \| 11.246 \| 6.76389<br><br>This study is classified as **Acceptable/Non-Guideline.** There is too much variability in the ChE data to make meaningful comparisons for sensitivity for RBC and brain ChE inhibition. Although there is little confidence in the ChEI data in this study, no additional acute CCA study is being requested at this time. **UPDATE: another acute CCA study report was identified (MRID 48773401a); see below.** |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | |
|---|---|---|
| **Guideline No./ Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| Special studies Comparative cholinesterase acute CCA<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain | 48773401a (2012) Acceptable/Non-guideline. 0, 5, 10, 50 or 200 mg/kg/day single gavage dose (1% aqueous methylcellulose; 10 mL/kg) young adult, PND 11 pups, PND 21 pups | The NOAEL for adult rats (both sexes) for RBC and brain cholinesterase inhibition following an acute oral dose was not determined. The LOAEL for adult rats is 10 mg/kg.<br><br>The NOAEL for PND 21 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg.<br><br>The NOAEL for PND 11 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg. |

| TCVP/Study | Sex/Age | Compartment | BMD Results (mg/kg) | |
|---|---|---|---|---|
| | | | $BMD_{10}$ | $BMDL_{10}$ |
| MRID 48773401a Acute CCA | Male PND11 | Brain | 5.1 | 4.5 |
| | Female PND11 | Brain | 5.9 | 4.8 |
| MRID 48773401a Acute CCA | Male PND11 | RBC | 5.0 | 4.1 |
| | Female PND11 | RBC | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | Male PND21 | Brain | 3.5 | 3.2 |
| | Female PND21 | Brain | 5.3 | 3.7 |
| MRID 48773401a Acute CCA | Male PND21 | RBC | 3.2 | 2.8 |
| | Female PND21 | RBC | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Male Adult | Brain | 7.4 | 5.6 |
| | Female Adult | Brain | 11.6 | 9.8 |
| MRID 48773401a Acute CCA | Male Adult | RBC | 6.5 | 3.6 |
| | Female Adult | RBC | 14.9 | 11.2 |

| | | |
|---|---|---|
| Special studies Comparative cholinesterase<br><br>*repeat CCA*<br><br>(Crl:CD(SD)IGS BR VAF/Plus strain rat) | 48773401 (2012) Acceptable/Non-guideline.<br>0, 5, 10, 50 or 200 mg/kg/day for both ages. | The main purpose of this study was to determine whether there is differential sensitivity between young adults and PND 11 pups with respect to cholinesterase inhibition following repeat oral exposure (11 doses) to TCVP.<br><br>Table 1 shows the adult ChEI data (3 hours after last dose) and Table 2 shows the pup ChEI data. There was a dose-related reduction in RBC and brain cholinesterase activity in both sexes and both age groups |

**Table 1. Inhibition (%) of RBC and Brain ChE Activity in Adult Rats (repeat)**

| Dose (mg/kg/day) | Males | Females |
|---|---|---|
| **RBC** | | |
| 5 | 12% | 8% |
| 10 | 13%* | 8.7% |
| 50 | 30%** | 40%** |
| 200 | 36%** | 62%** |
| **Brain** | | |
| 5 | 2% | - |
| 10 | 7% | 12%* |
| 50 | 14.9%** | 42%** |
| 200 | 17.8%** | 57%** |

**Table 2. Inhibition (%) of RBC and Brain ChE Activity in Pups (repeat)**

| Dose (mg/kg/day) | Males | Females |
|---|---|---|
| **RBC** | | |
| 5 | 2% | - |
| 10 | 2% | - |
| 50 | 33%** | 19%** |
| 200 | 60%** | 62% |
| **Brain** | | |
| 5 | 4% | 4% |
| 10 | 6% | 6% |
| 50 | 16%** | 18.7%** |
| 200 | 46%** | 45%** |

RBC ChE inhibition. At 50 mg/kg/day, both male pups and male adults had similar levels of inhibition (30% to 33%), whereas at 200 mg/kg/day, the male pups were inhibited to ≈60% compared to 36% in the male adult rats. At 50 mg/kg/day, adult females demonstrated more inhibition (≈40%) than the female pups (19%) but at 200 mg/kg/day, both female pups and female adults had ~62% inhibition.
Brain ChE inhibition. Adult females displayed greater brain ChE inhibition at all dose levels than the adult males, whereas a similar magnitude of brain ChE inhibition was observed in male and female pups. Adult females displayed brain ChE inhibition at all dose levels.
A benchmark dose analysis of the cholinesterase data (RBC and brain) was performed that provides both the $BMD_{10}$ and $BMDL_{10}$ of adults and PND11 pups.

**$BMD_{10}$s and $BMDL_{10}$s for Adult Rat and PND 11 Pup Cholinesterase**

| | RBC $BMD_{10}$ | RBC $BMDL_{10}$ | Brain $BMD_{10}$ | Brain $BMDL_{10}$ |
|---|---|---|---|---|
| Adult ♂ | 7.7178 | 3.5942 | 33.803 | 24.4489 |
| Adult ♀ | 8.6762 | 6.1335 | 7.1764 | 5.4980 |
| PND 11 ♂ | 20.4688 | 15.9719 | 33.4825 | 26.5707 |

| Table A.2.2 Subchronic, Chronic and Other Toxicity Profile of Tetrachlorvinphos (TCVP) | | | | | | |
|---|---|---|---|---|---|---|
| Guideline No./ Study Type | MRID No. (year)/ Classification /Doses | Results | | | | |
| | | PND 11 ♂ | 20.5608 | 13.1692 | 24.2224 | 18.9412 |
| | | *Overall conclusion.* The main objective of this study was to determine if the pups are more sensitive than the adults to the inhibitory potential of TCVP. Based on assignment of the NOAEL and LOAEL and the BMD modeling, there was no demonstration for increased sensitivity of the pups relative to the adults for either RBC or brain ChE. It is noted, however, that the magnitude of the high dose male pup brain and RBC ChE inhibition is greater than that in the adult males, but the significance is not established. | | | | |

## A.3 Hazard Identification and Endpoint Selection

### A.3.1 Acute Dietary Reference Dose (aRfD) – All Populations

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No**.: 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Data from the young rat from the acute CCA study are appropriate for acute POD derivation, since effects were observed after a single exposure and the endpoint is the most sensitive adverse response in all populations. The study provides the lowest POD following a single dose. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) results in an aPAD of 0.0028 mg/kg/day; the (FQPA) factor may be excluded for the sub-population of adults 50-99 (aPAD of 0.028 mg/kg/day).

### A.3.2 Steady State Reference Dose (ssRfD) –All Populations

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No.:** 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg/day associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Although the steady state dietary endpoint was selected from an acute dose comparative cholinesterase study, the duration of this study is considered appropriate for this exposure scenario since AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose. A longer-term exposure does not result in a lower POD, as evidenced by the larger $BMD_{10}$s found for the repeat dose CCA data.

The point of departure is protective of any exposure duration longer than 21-days, including chronic exposure, since cholinesterase inhibition does not increase after reaching maximum inhibition or steady state and occurs following one exposure to TCVP. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) results in an ssPAD of 0.0028 mg/kg/day; the (FQPA) factor may be excluded for the sub-population of adults 50-99 (ssPAD of 0.028 mg/kg/day).

### A.3.4 Incidental Oral Exposure (Steady-State)

**Study Selected:** Acute Comparative Cholinesterase Study - Rats
**MRID No**.: 49773401a
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 2.8 mg/kg associated with RBC ChE inhibition in male PND 21 pups was selected as a suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding $BMD_{10}$ was 3.2 mg/kg/day.
**Comments about Study/Endpoint/Uncertainty Factors:** Data from the young rat from the acute CCA study are appropriate for the incidental oral assessment since the AChE data across the TCVP database demonstrate that there is no progression of AChE inhibition over exposure duration, and steady state inhibition occurs essentially after a single dose, and the endpoint is the most sensitive adverse response in all populations. A UF of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for the FQPA safety factor (incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.5)) is appropriate for incidental oral exposures.

### A.3.6 Dermal Exposure

There is no potential hazard *via* the dermal route, based on the lack of treatment-related effects, including the lack of RBC and brain cholinesterase inhibition following repeat dermal exposure of rats at dose levels up to 1000 mg/kg/day, and there is no concern for quantitative susceptibility.

### A.3.7 Inhalation Exposure (Steady State)

**Study Selected:** 28-day Inhalation Toxicity Study
**MRID No**.: 48803501
**Dose and Endpoint for Risk Assessment:** A $BMDL_{10}$ of 0.02 mg/L/day associated with RBC ChE inhibition in both sexes, following inhalation exposure, was selected as a suitable POD for assessing the potential risk associated with inhalation exposure (single day and steady-state). The corresponding $BMD_{10}$ was 0.12 mg/L/day.

**Comments about Study/Endpoint/Uncertainty Factors:** A route-specific, 28-day inhalation toxicity study was used for the steady-state inhalation assessment. Using the Agency's Reference concentration (RfC) methodology, human equivalent concentrations (HECs) and Human

Equivalent Doses (HEDs) was calculated for residential and occupational handlers. Since the inhalation POD is based on a route-specific toxicity study, no absorption factor is necessary to estimate exposure. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

A total uncertainty factor of 30X is appropriate for inhalation exposures [3X for interspecies extrapolation, 10X for intraspecies variation] for adult males and females 49+. The FQPA safety factor (10X) will be retained for infants, children, youths, and women of child-bearing age for all exposure scenarios to account for uncertainties introduced by the lack of sufficient data to quantify potential neurodevelopmental effects observed in epidemiology data on the OP, chlorpyrifos.

## A.4 Executive Summaries

### A.4.1 Subchronic Toxicity

#### 870.3100 90-Day Oral Toxicity – Rat

In a subchronic oral toxicity study (MRID 43371201), tetrachlorvinphos (TCVP; 99% a.i.; Batch KMJ 012) was given to Sprague Dawley rats (10/sex/group) in the diet at doses of 0, 100, 2000, or 5000 ppm (0, 6.7, 142, and 375 mg/kg/day for males; 0, 10.0, 197, and 467 mg/kg/day for females) for 13 weeks.

Survival was not adversely affected in either sex, and there were no clinical signs of toxicity. There were no effects on body weight in the females, but decreased body weight (7%-12%) was observed in males at 5000 ppm throughout the study.

Red blood cell (RBC) cholinesterase (ChE) inhibition was observed in males at 2000 ppm (30%) and 5000 ppm (72%) and in females at 2000 ppm (79%) and 5000 ppm (91%). A noteworthy finding was that 2 rats/sex at 5000 ppm had no measurable RBC ChE activity at 13 weeks. Brain cholinesterase inhibition was observed in females at all dose levels (12%, 14%, 24%, with increasing dose), but statistical significance was not attained at any dose level. Brain cholinesterase inhibition was not observed in males.

Liver weight was increased in females at 2000 ppm (22% when adjusted for body weight) and at 5000 ppm 22%-28%, actual and adjusted). Males displayed an increase in adjusted liver weight (8% and 19% at 2000 ppm and 5000 ppm, respectively). Increased kidney weights were observed in males at 5000 ppm (18% adjusted for body weight), and increased adrenal weights (actual/adjusted) were observed in females at 2000 ppm (20%/28%) and 5000 ppm (28%/32%). There was a dose-related increase in the incidence and severity of bilateral basophilic tubules of the kidneys in males and in the incidence of cellular alteration (fat deposition) in the adrenal cortex of females at 2000 ppm (7/10) and 5000 ppm (9/10). All females at 2000 ppm and 5000 ppm displayed centrilobular hepatocellular hypertrophy, with the severity increasing with dose. In males, the incidence of hepatocellular hypertrophy was significantly increased at 2000 ppm (8/10),

with 2 displaying general cell enlargement, whereas only 1/10 males at 5000 ppm displayed hepatocellular hypertrophy and 7/10 displayed general cell enlargement in the liver. There was a dose-related increase in the incidence of thyroid follicular cell hypertrophy in both sexes.

The NOAEL is 6.7 mg/kg/day, based on RBC ChEI in both sexes (males 30%*; females 79%**), bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females, higher adjusted liver weights (both sexes), higher adjusted adrenal weights in females, and thyroid follicular cell hypertrophy in both sexes at the LOAEL of 142 mg/kg/day. At 467 mg/kg/day, decreased body weight was observed throughout the study in males (7%- 12%), with the magnitude of the deficit increasing over time, females had a 24% brain cholinesterase activity inhibition, although statistical significance was not attained (females 12%, 14%, 24% brain ChEI with increasing dose; males 1% at HDT), and both sexes displayed RBC ChEI (males 72%; females 91%).

This study is classified as Acceptable/Guideline, and it satisfies the guideline requirement (OCSPP 870.3100; OECD 408) for a subchronic oral toxicity study in the rat.

**Single Day and 21-Day Oral Toxicity – Rat**

In a 21-day oral toxicity study (MRID 45570601), tetrachlorvinphos (99.1% a.i., lot #801066) was administered to 18 Crl:CD®(SD)IGS BR rats/sex/dose by gavage at dose levels of 0, 8, 12, 20, or 50 mg/kg/day. Seven or eight animals/sex/group were ***sacrificed approximately 3.5 hours following the first dose*** (time to peak effect); the remaining 10/sex/group were killed after an additional 21 days of dosing. Blood samples were taken for plasma and RBC cholinesterase (ChE) determinations approximately one week prior to study initiation, 3.5 hours following dosing on the first day (day 0), on study days 1, 7, and 14, and at study termination (day 21). Whole brain ChE levels were measured after sacrifice on days 0 and 21.

No treatment-related clinical signs of toxicity or deaths were observed in any animal during daily observations or 1 hour post-dosing. Body weights were similar between the treated and control groups throughout the study.

Dose-related inhibition of ChE activity was observed following both acute and repeated exposures. Inhibition in females occurred at a lower dose than in males. Following a single dose of 50 mg/kg, inhibition of plasma ChE activities (63-67%) relative to concurrent controls were observed in males and females. Also significant inhibition (37-46%) of plasma ChE activities were observed in males and females at 20 mg/kg and in females at 12 mg/kg. However, the LOAEL for plasma ChE inhibition was 8 mg/kg based on inhibition of plasma ChE activity relative to pretest values in males. The NOAEL for plasma ChE inhibition was not established. Significant inhibition (37-46%) of RBC ChE activities from both sexes were observed at 50 mg/kg only. Significant inhibition of whole brain ChE was observed n males at 50 mg/kg (54%) and 20 mg/kg (22%) and in females at 50 mg/kg (23%).

Following repeated exposure, plasma ChE activity in the 20- and 50-mg/kg/day males was similar to the concurrent control levels at each time point with the exception of the high-dose males on day 1 (25% inhibition). However in females, plasma ChE activity was significantly inhibited by 26-30% in the 8-mg/kg/day group beginning on day 14 and by 23-67% in the 12-, 20- and 50-mg/kg/day groups beginning on day 1. Inhibition of RBC ChE levels in 50-mg/kg/day males and females was transient with a maximum inhibition at day 7 (44% and 57%, respectively) followed by modest recovery in males and slight recovery in females. Whole brain ChE activity in males was not affected by repeated exposure. In contrast, significant inhibition of brain ChE activities were observed in the 50 mg/kg/day (36%) and 20 mg/kg/day (16%) females.

**Following both a single and 21-day repeated dose of tetrachlorvinphos, the LOAEL for brain ChE inhibition was 20 mg/kg, based on inhibition of brain ChE activity in males with a NOAEL of 12 mg/kg.**

**Following a single dose of tetrachlorvinphos, the LOAEL for erythrocyte ChE inhibition was 50 mg/kg, based on inhibition of erythrocyte ChE activity with a NOAEL of 20 mg/kg.** Because reproducibility of ChE activity of the rat RBC samples was poor and the standard deviations were large for all groups, the RBC ChE inhibition measurements in the 21-day toxicity study were judged to be unreliable. Therefore, the HIARC (TXR# 0050548; dated March 7, 2002) concluded not to use RBC ChE data from this 21-day study due to lack of confidence in the results.

**Following single and repeated exposure to tetrachlorvinphos, the LOAEL for plasma ChE inhibition was 8 mg/kg, based on inhibition of plasma ChE activity relative to pretest values in males. The NOAEL for plasma ChE inhibition was not established.**

This study is classified as Acceptable/non-Guideline, and it does not satisfy any guideline requirement.

**870.3150 90-Day Oral Toxicity - Dog**

No subchronic study.

**870.3200 21/28-Day Dermal Toxicity - Rat**

In a repeat dose dermal toxicity study (MRID 41342001), male and female Crl:CD BR rats (5/sex/dose) received dermal applications of 0, 10, 100, or 1000 mg/kg/day Rabon Technical (TCVP; 99% a.i.; ) moistened with deionized water for 6 hours/day, 5 days/week for a total of 15 treatments over a 21-day period.

Rabon Technical did not induce significant dermal effects at dose levels up to and including 1000 mg/kg/day. Treatment caused a statistically significant decrease in plasma cholinesterase activity in females at 1000 mg/kg/day. Plasma cholinesterase was also lower than control values for males at the mid and high doses and females at the mid dose; these differences were not statistically significant. TCVP did not result in brain or RBC AChE inhibition, and there were no adverse effects on mortality, body weight, food consumption, hematology, clinical chemistry, organ

weights, or gross and histopathology. The NOAEL is established at 1000 mg/kg/day (the limit dose), since plasma cholinesterase inhibition is not considered a relevant adverse endpoint.

This study is classified as Acceptable/non-Guideline. The study does not satisfy the guideline requirement (OCSPP 870.3200) for a repeat dose dermal toxicity study since an inadequate number of animals per dose were tested; however, the study is adequate for the determination that a dermal risk assessment is not required for TCVP.

### 870.3465 Subchronic Inhalation – Rat

In a nose-only inhalation toxicity study (MRID 48803501), tetrachlorvinphos (TCVP; Lot No. TX 100113; 100% purity) aerosol was administered to male and female Sprague-Dawley rats (10/sex/concentration) for 6 hours/day, 5 days/week for 3 weeks at exposure concentrations of 0, 0.05, 0.5, or 1.0 mg/L. During the final week of exposure (week 4), the animals were exposed for 7 days. An additional 10 rats/sex/concentration were included in the control and high dose groups and sacrificed 14 days after completion of the 28-day exposure period to determine the reversibility of any effects observed. Actual exposure concentrations as measured by HPLC were 100%, 100%, and101% of target values. The mass median aerodynamic diameters (MMADs) ± geometric standard deviations (GSD) were 2.57 µm ±3.785, 4.51 µm ±3.541, and 4.27 µm ±3.343 for the low-, mid- and high concentrations, respectively.

There were no treatment-related deaths. Treatment-related reduced body weights (↓7%* and ↓8%**) and body weight gains (↓27%** and ↓34%***) were observed in males from the mid- and high exposure groups, respectively. The body weight difference persisted through the recovery period in the high-exposure (↓12%) male recovery group, but the weight gain during those 2 weeks was slightly higher (5%) relative to the control group. Bodyweight was comparable among the female groups throughout the study. Body weight gain was reduced in mid- (↓23%) and high (↓32%) exposure females, but body weight gain was comparable to the control during the recovery period. Food consumption was decreased throughout the study in the mid- and high male groups and during the first two weeks in the low dose male group, whereas food consumption was comparable among the female groups. There were no treatment-related findings during the ophthalmoscopic examinations. Decreased hemoglobin concentration and increased platelets were noted in high exposure concentration females, but these findings were no longer evident at the end of the 2-week recovery period. Calcium was slightly, but significantly, elevated in males at all three exposure levels, but there was no dose-response. Cholesterol was significantly elevated in females from the mid- (↑22%) and high (↑27%) exposure groups. These findings were not observed in the recovery group.

Statistically significant RBC ChE activity inhibition ($p<0.001$) was observed in females at the mid- and high exposure concentrations (35% and 30%, respectively). Statistically significant AChE and RBC ChE activity inhibition ($p<0.001$) was observed in males at the mid- and high exposure concentrations (38% and 31% for AChE, respectively; 24% and 31% for RBC ChE, respectively). Plasma acetylcholinesterase activity (58% to 70%) and plasma butyrylcholinesterase activity (66% to 87%) were decreased relative to controls at all exposure

concentrations in females. All cholinesterase activities were lower relative to controls in the male and female recovery groups, but the differences were not statistically significant.

Treatment-related gross findings were limited to discoloration and enlargement of the adrenal glands at the mid- and high exposure concentrations in males, and in females at all exposure concentrations. Diffuse adrenal cortical cell vacuolation (minimal to moderate with an exposure-related incidence) was observed in both males and females at all exposure concentrations. Minimal follicular cell hypertrophy of the thyroid gland was observed with an exposure-related incidence in both sexes at the mid- and high exposure concentrations. Minimal to mild ovarian interstitial cell vacuolation was observed with an exposure-related incidence in females at the mid- and high exposure concentrations. The findings in the thyroid and ovary were referred to as "commonly observed in this strain and age of rat," but no historical control data or literature citations were provided. In the recovery group, 2/5 males and 2/5 females at the high dose had minimal diffuse adrenal cortical cell vacuolation (0/5 incidence in recovery controls). No other treatment-related microscopic findings were observed in the recovery group.

**Based on the effects seen in this study, a systemic NOAEL in male and female Sprague-Dawley rats was not identified. The systemic LOAEL in male and female rats was 0.05 mg/L, based on diffuse adrenal cortical cell vacuolation in both sexes, enlarged adrenals in females, and increased adrenal weights in females. At 0.5 mg/L and 1.0 mg/L, in addition to the adrenal findings, there was a dose-related increase in vacuolation of the ovaries in females, an increase in squamous metaplasia of the larynx in both sexes, and an increase in follicular cell hyperplasia of the thyroids in both sexes.**

**The NOAEL for cholinesterase inhibition was 0.05 mg/L, based on an increase in RBC cholinesterase inhibition in both sexes at 0.5 mg/L/day. Brain cholinesterase activity was not monitored.**

The RBC cholinesterase data from this study have been evaluated using benchmark dose modeling techniques. The results are shown below.

| **$BMD_{10}$/$BMDL_{10}$ Results (mg/L)** | | | |
|---|---|---|---|
| **Sex/Age** | **Compartment** | **$BMD_{10}$** | **$BMDL_{10}$** |
| Female | RBC | 0.394 | 0.050 |
| Male | RBC | 0.122 | 0.022 |

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for a repeat dose inhalation toxicity study.

COMMENT: Although a no effect dose was not identified for the findings in the adrenal (LOAEL 8.7 mg/kg/day), when compared on a mg/kg/day basis to the $BMDL_{10}$ (95% lower confidence limit on the $BMD_{10}$) established for cholinesterase inhibition, the point of departure



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(POD; 1.31 mg/kg/day) used in the inhalation exposure risk assessment is protective of these adrenal findings.

### A.4.2 Prenatal Developmental Toxicity

#### 870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 40152701), tetrachlorvinphos (98.6% ai; Lot No. 10-56-0-0) was administered *via* gavage to groups of 25 Sprague-Dawley Crl:COBS®CD®(SD)BR pregnant rats/groups at dose levels of 0 (0.5% methyl cellulose), 75, 150, or 300 mg/kg/day from gestation day (GD) 6 through GD 15.

All dams survived until study termination. At 300 mg/kg/day, one dam displayed tremors from day 10 onward, and chromodacryorrhea was observed only at this dose level. Although body weights were comparable among the groups, body weight gains were significantly reduced at 300 mg/kg/day throughout the dosing period (52%), and food consumption was also reduced. The numbers of corpora lutea, implantations, resorptions, and dams with liable fetuses were comparable among the groups. The mean number of live fetuses, sex ratio, and fetal body weights were comparable among the groups.

The maternal NOAEL is 150 mg/kg/day, and the maternal LOEL is 300 mg/kg/day, based on tremors and an increased incidence of chromodacryorrhea.

The developmental NOAEL is 300 mg/kg/day, the highest dose tested. A developmental LOAEL was not determined.

The developmental toxicity study in the rat is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; 83-3a) in the rodent when combined with MRID 41828001, MRID 41967201, and MRID 42520101. NOTE: The maternal NOAEL/LOAEL differ from the original assessment due to the current policy that decreases in body weight gain without significant reduction in body weight is not considered an adverse effect.

#### 870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a prenatal developmental toxicity study (MRID 00127831), New Zealand White rabbits (#/sex/dose) were administered tetrachlorvinphos (98% a.i.; T-142-3) by gavage at doses of 0, 150, 375, or 750 mg/kg/day in 5 mL/kg carboxy methylcellulose on gestation days 6-19.

Maternal toxicity at the highest dose tested was manifested as mortality (0/18, 1/18, 1/8, 2/18), abortions (0, 1, 0, 3), and red vaginal fluid (0, 1, 1, 8) in the control, low, mid, and high-dose groups, respectively.

**The maternal NOEL is 375 mg/kg/day, and the maternal LOEL is 750 mg/kg/day.**

Developmental toxicity at the highest dose tested was manifested as an increase in early resorptions/dam (0.4, 0.5, 0.3, 1.4), with a corresponding increase in postimplantation loss (10.6%, 5.6%, 10.5%, 21.9%) and a decrease in live fetuses/dam (7.7, 7.8, 6.9, 5.8) for the control, low, mid, and high-dose groups, respectively.

**The developmental NOEL is 375 mg/kg/day, and the developmental LOEL is 750 mg/kg/day.**

This developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; 83-3b) in rabbits.

### A.4.3 Reproductive Toxicity

#### 870.3800 Reproduction and Fertility Effects - Rat

In a 2-generation reproduction study (MRID 00127831), 28 Charles River CD Crl: (SD) BR Sprague Dawley rats/sex/dose were administered tetrachlorvinphos (99% a.i.; technical Rabon) *via* the diet at doses of 0, 100, 500, or 2000 ppm (F0 males: 0, 5.2, 26, or 102 mg/kg/day/F0 females: 0, 7.3, 40, or 155 mg/kg/day; F1 males: 0, 6.7, 34, or 130 mg/kg/day/F1 females: 0, 8.3, 43, or 168 mg/kg/day). Treatment of the F0 rats began when they were approximately 6 weeks old, and after 10 weeks, they were bred to produce F1 animals. Treatment continued throughout the mating, gestation, and lactation periods, with termination of the F0 rats after weaning of their litters. The F1 rats were weaned onto the same diets as their parents, and groups of 24 rats/sex/dose were selected as the F1 generation. The F1 rats were treated for 11 weeks and then mated to produce F2 litters. Treatment also continued throughout the mating, gestation, and lactation periods. Termination of the F1 and F2 animals occurred at the time of weaning of the litters.

There was no adverse effect on survival, and no clinical signs of toxicity were observed in either generation. Body weights of the adult animals were not adversely affected in either generation. Increased adrenal weights in the F0 females at 2000 ppm were considered treatment-related, although a similar increase in adrenal weight was not observed in the F1 females or in males of either generation. Fertility indices, duration of gestation, mean number of implantation sites, number of stillborns, mean litter size, pup survival, and pup body weights were comparable among the groups in both generations.

**The parental NOAEL is 500 ppm (males 26/females 40 mg/kg/day). The parental LOAEL is 2000 ppm (males 102/females 155 mg/kg/day), based on increased adrenal weights of F0 females**.

**The offspring NOAEL is 2000 ppm (males 102/females 155 mg/kg/day). The offspring LOAEL was not identified.**

**The reproductive NOAEL is 2000 ppm (males 102/females 155 mg/kg/day). The reproductive LOAEL was not identified.**

Note: Although minimal toxicity was observed, and higher doses would have been tolerated, cholinesterase measurements were not performed in this study. Based on findings in other studies in the TCVP database, cholinesterase inhibition would have been observed in this study, if monitored, at the mid and high dose levels.

The 2-generation reproduction toxicity study in the rat is classified Acceptable/Guideline, and it satisfies the guideline requirement for a reproduction toxicity study (OCSPP 870.3800; OECD 416) in the rodent.

### A.4.4 Chronic Toxicity

#### 870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic toxicity/carcinogenicity study (MRID 42980901/43335101), groups of Sprague-Dawley rats (50/sex/group) were administered tetrachlorvinphos (99% a.i.) *via* the diet at dose levels of 0, 100, 1000, or 2000 ppm (males 0, 4.23, 43.2, or 88.5 mg TCVP/kg/day; females 0, 5.93, 62.7, or 125.3 mg TCVP/kg/day) for two years.

Survival was comparable among the groups in both sex, and there were no treatment-related clinical signs of toxicity. Body weight was comparable among the male groups, and females at the high dose displayed slightly lower body weights (8%-12%) than the controls from week 10 on (12% at 52 weeks; 8% at 104 weeks). Food consumption was comparable among the groups.

Females at 2000 ppm had significantly elevated cholesterol levels at weeks 77/78 and 104. Effects at 1000 and 2000 ppm in both sexes included an increased incidence and tendency to greater severity of diffuse lipidosis of the adrenal zona fasciculata, hypertrophy of periacinar hepatocytes, centriacinar degenerative (males only) changes of the liver, and reduced alkaline phosphatase activity.

RBC cholinesterase inhibition was observed in females at 1000 ppm (29%*) and 2000 ppm (36%**) at week 77/78; 18% and 22% at week 103/104 (not **). Brain cholinesterase inhibition was observed in females at 52 and 104 weeks was 17% and 16% (not **). BMDs were not run due to lack of dose-response in both compartments.

The systemic toxicity NOAEL is 100 ppm (4.23/5.93 mg/kg/day). The systemic toxicity LOAEL is 1000 ppm (43.2/62.7 mg/kg/day), based on histological liver (hypertrophy of periacinar hepatocytes in both sexes and centriacinar degenerative change in males) and adrenal changes (increased incidence of diffuse lipidosis of adrenal zona fasciculata in both sexes).

Increased incidence of thyroid C-cell adenomas was observed in male rats at the highest dose and adrenal pheochromocytomas were observed in males.(both sexes). The LEL is 1000 ppm, based on decreased body weight in females, histological liver and adrenal changes in both sexes.



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The study is classified Acceptable/Guideline, and it satisfies the guideline requirements for a combined chronic toxicity/carcinogenicity study (OCSPP 870.4300; OECD 453), a chronic oral toxicity study (870.4100; OECD 452), and a carcinogenicity study (870.4200; OECD 451) in the rodent.

#### 870.4100b Chronic Toxicity – Dog

In a chronic oral toxicity study (MRID 42679401), tetrachlorvinphos (TCVP; 99% a.i.; Batch 01-KMJ-012) was given to outbred Beagle dogs (4/sex/group) *via* capsule at doses of 0, 6.25, 500, or 1000 mg/kg/day for 52 weeks.

Survival was not adversely affected in either sex, and there were no clinical signs of toxicity. There were no treatment-related effects on body weight or food or water consumption, and no differences in ophthalmologic, macroscopic, and microscopic findings in either sex.

Treatment-related decreases in red blood cell counts at 500 and 1000 mg/kg/day were corroborated by decreases in hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit, and increases in mean corpuscular volume. The kidney and liver weight increases at 500 and 1000 mg/kg/day in both sexes may be related to the alkaline phosphatase increases (both sexes) and cholesterol decreases (males) observed, but no histopathological correlates were evident. The decreases in urine specific gravity at 500 and 1000 mg/kg/day in both sexes may be related to the kidney weight increases at these dose levels, but histopathological correlates were not evident.

RBC and brain cholinesterase inhibition were not observed at any dose level in either sex at any time point monitored.

The systemic toxicity NOAEL is 6.25 mg/kg/day. The systemic toxicity LOAEL is 500 mg/kg/day, based on decreased red blood cell counts, hemoglobin, hematocrit, MCHC, MCV, alkaline phosphatase, urine specific gravity, and decreased liver and kidney weights.

The chronic toxicity study is classified Acceptable/Guideline, and it satisfies the guideline requirement for a chronic toxicity study (OCSPP 870.4100; OECD 452) in the non-rodent.

### A.4.5 Carcinogenicity

#### 870.4200a Carcinogenicity Study – Rat

In the combined chronic toxicity study (MRID 42980901/43335101), groups of 50 male and 50 female Charles River Sprague-Dawley rats received TCVP in their diet over a 2-year period at 0, 100, 1000 or 2000 ppm (equivalent to 0, 4, 43 and 89 mg/kg/day in males and 0, 6, 63 and 125 mg/kg/day in females, respectively). See above under 870.4100a.

There were increases in the incidences of thyroid C-cell adenomas and adrenal pheochromocytomas in male rats only. Neither of these increases were statistically significant by pairwise comparison to controls, but there was a statistically significant increasing trend for the adrenal tumors.

This study is classified as Acceptable/Guideline, and it satisfies the guideline requirements (870.4200; OECD 451] for a carcinogenicity study in the rat.

In another rat study (MRID 00117443; 1978 NCI-sponsored Gulf South study), Osborne-Mendel rats received TCVP in their diet at doses of 0, 4250, or 8500 ppm for 80 weeks, followed by 31 weeks observation.

Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid.

This study is classified Acceptable/Non-Guideline, and it does not satisfy the guideline requirement (870.4200; OECD 451) for a carcinogenicity study.

### 870.4200b Carcinogenicity – Mouse

In a carcinogenicity study (MRID 00126039), B6C3F1 mice were fed diets containing 0, 17.5, 64, 320, 1600, 8000, or 16000 ppm tetrachlorvinphos for two years in a carcinogenicity study. For systemic toxicity, the NOAEL was 1600 ppm (240 mg/kg/day) and the LOAEL was 8000 ppm (1200 mg/kg/day), based on decreased weight gain. Administration of TCVP in the diet to B6C3F1 mice resulted in statistically significant increases in hepatocellular adenomas, carcinomas and combined adenomas/carcinomas (with carcinomas predominant) in females, and in combined hepatocellular adenomas/carcinomas in males. In male mice there were also statistically significant increases in renal adenomas, carcinomas and combined adenomas/ carcinomas. The statistically significant increases in tumors noted above, all occurred only at doses of TCVP of 8000 ppm or greater, except for the combined hepatocellular adenomas/ carcinomas in female mice, which also occurred at 1600 ppm.

This study is classified as Acceptable/guideline, and it satisfies the guideline requirements (870.4200; OECD 451] for a carcinogenicity study in the mouse.

In another carcinogenicity study (MRID 00117443), B6C3F1 mice were fed diets containing 0, 8000, or 16000 ppm TCVP for 80 weeks, followed by 12 weeks observation. Increased incidences of hepatocellular carcinomas and granulomatous lesions of the liver were found in the dosed mice.

This study is classified Acceptable/Non-Guideline, and it does not satisfy the guideline requirement (870.4200; OECD 451) for a carcinogenicity study in the mouse.

## A.4.6 Mutagenicity

| Summary of the Genotoxicity Studies for TCVP | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| **GENE MUTATION** | | | |
| 870.5100 | Bacterial Reverse Gene Mutation Assay in *Salmonella typhimurium* | 4122508 (1989)<br><br>Acceptable/guideline<br><br>0, 10-667 µg/plate -S9<br>0, 66.7-3300 µg/plate +S9 | **Negative** up to cytotoxic concentrations at the highest dose tested +/-S9 |
| **CHROMOSOME ABERRATIONS** | | | |
| 870.5375 | *In vitro* Mammalian Cell Clastogenicity Assay in Chinese hamster ovary (CHO) cells | 41312901 (1989)<br><br>Acceptable/guideline<br><br>0, 29.9, 44.9, 59.9, 79.8, 99.8 µg/mL -S9 (20-hr cell harvest)<br>0, 12.5, 25, 37.6, 75.1 µg/mL, +S9 (10-hr cell harvest) | **Positive** Significant & dose-related increases in chromosome aberrations in the absence of S9 only after a prolonged exposure due to severe mitotic delay, unhealthy monolayers and reduced mitotic cells at 59.9 & 79.8 µg/mL. Major aberrations: chromatid & chromosome breaks<br>NOTE: Increases in chromosome aberrations were accompanied by marked increases in chromatid & chromosome gaps.<br><br>**Negative** with S9 activation up to a precipitating (≥676 µg/mL) & cytotoxic (2030 µg/mL) concentrations |
| | *In vitro* Mammalian Cell Clastogenicity Assay in Mouse spleen cells | Amer & Aly (1992)<br><br>Acceptable/nonguideline<br>0.25, 0.5, 1.0, 2.0 µg/mL (4-hr treatment) | **Chromosome aberrations**<br>**Positive:** Significant & dose-related increases in chromosome aberrations (minus gaps) at ≥0.5 µg/mL Major aberrations: chromatid & chromosome fragments<br>NOTE: Increases in chromosome aberrations were accompanied by marked increases in chromatid & chromosome gaps.<br><br>**Sister Chromatid Exchange (SCE)**<br>**Positive:** Significant & dose-related increases in SCE induction at ≥0.5 µg/mL |

| Summary of the Genotoxicity Studies for TCVP | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID No. (year)/ Classification /Doses** | **Results** |
| | Micronucleus Assay in Bone Marrow Cells of the Mouse | Amer & Aly (1992)<br><br>**Oral:** 0, 3000 & 6000 ppm dietary administration daily for 14 consecutive days or 10 weeks<br>**Ip injection**: 0, 50 & 100 mg/kg weekly for 2 weeks<br>**Dermal:** 0, 1350 mg/kg 4 treatments | **ORAL:** S↑ % PCEs at 3000 & 6000 ppm after 10 weeks at 24 hours & 7 & 14 days post-treatment but **S↑% MPCEs only 6000-ppm group at 24 hours & 7 days post-treatment**<br><br>**IP INJECTION**:<br><br>**<u>50 mg/kg</u>: S↑ % MPCEs at 24 hr. post-treatment (Double injection only); % PCEs not reported.**<br><br>**<u>100 mg/kg</u> (single injection): S↑ % PCEs at 24 hr. post-treatment only.**<br><br>**<u>100 mg/kg</u> (double injection): S↑ % PCEs at 24 hr. post-treatment**<br>**S↑ % MPCEs at 24 hr. post-treatment only.**<br><br>**DERMAL:** S↑ % PCEs at 24 hr. post-treatment 1350 mg/kg (4 applications) only; no increase in MPCEs |
| **OTHER MUTAGENIC MECHANISMS** | | | |
| 870.5550 | *In vitro* unscheduled DNA synthesis (UDS) in primary rat hepatocytes | 42156401 (1992)<br><br>Acceptable/guideline<br><br>0, 10-40 µg/mL (9 doses) | **Negative**<br>Cytotoxicity was observed as follows: 35 & 40 µg/mL -lethal<br>23-30 µg/mL (moderate to high cytotoxicity)<br>15 & 20 µg/mL (slight cytotoxicity)<br>10 µg/mL (non-cytotoxic) |
| | DNA adduct formation<br>Swiss male mice<br>liver. | Zayed et al., 1983)<br>25, 50 and 100 mg/kg i.p. injection | **Positive**<br>Fraction of total applied dose associated with 7-methyl guanine was estimated to be $9x10^{-5}$ and $39x10^{-5}$ in DNA and RNA, respectively |

The relevance of the mutagenic findings to the tumorigenic response seen in female mice cannot be established. Therefore, a follow-up mouse micronucleus assay (OPPTS Harmonized Guideline 870.5395) is required for TCVP. Additionally, a study that investigates possible genotoxic activity in the target organ (liver) is required. This study should examine DNA damage potential (Comet assay, DNA adduct formation, or any other DNA target)[41].

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[41] N. McCarroll and D. Davis, 12/21/2016, Tetrachlorovinphos (TCVP): Revisit of Mutagenicity Studies, TXR#0057553, D437226.

## A.4.7 Neurotoxicity

### 870.6100b Delayed Neurotoxicity – Hen

In an acute delayed neurotoxicity study in hens (MRID 41905901), technical Rabon (tetrachlorvinphos; Lot # 01-KMJ-012; 99% a.i.), was administered twice orally (Mazola corn oil) to hens at 2500 mg/kg, with an intervening 21-day period (total dose 5000 mg/kg).

There was sufficient evidence of acute toxicity, including mortality (4/15), to establish that the test material was administered at a sufficiently high dose. TCVP did not result in delayed neurotoxicity, as evidenced both by in-life observations and microscopic examination of spinal cord tissue from three levels. The minimum myelin degeneration seen in 2 hens was consistent with the normal background incidence for this finding in this type of study. The positive control material (tri-0-tolyl- phosphate, TOTP) at 1000 mg/kg elicited the appropriate response.

This study is classified **as Acceptable/Guideline** and it satisfies the guideline requirement for a delayed neurotoxicity study in the hen (870.6100).

### 870.6200a Acute Neurotoxicity Screening Battery – Rat

In an acute neurotoxicity study (MRID 42912501), tetrachlorvinphos (99% a.i.; Lot #: 01-KMJ-012) was administered *via* gavage (10 mL/kg; in corn oil) to non-fasted Sprague-Dawley Crl:CD®BR rats (12/sex/dose) at doses of 0, 65, 325, or 650 mg/kg. All rats were evaluated in functional observational batteries and motor function observations on days 0, 7, and 14.

Transient neurotoxic effects were observed in both sexes on day 0 at the mid- and high-dose levels. These effects were consistent with cholinesterase inhibition. At 650 mg/kg, the predominant clinical signs observed in both sexes on the day following dosing consisted of gait alterations (prostration, rocking, lurching, and swaying when ambulatory; walked on tiptoes), constricted pupils, tremors (fore- and hindlimb), cool body to the touch, yellow material on various body surfaces, red material on forelimbs, around eyes, nose, and mouth, and/or increased defecation. Several of these findings were noted in a limited number of rats (mainly females) on days 2, 3, 4, and/or 5. At 325 mg/kg, one female showed gait alterations and one male and 3 females had constricted pupils on day 1. The neuropathologic examination gave no indication of any dose-related permanent effects on the brain or in the peripheral or central nervous tissues, consistent with the lack of permanent changes in muscular coordination and/or behavior.

The NOAEL is 65 mg/kg, and the LOAEL is 325 mg/kg, based on transient neurotoxic effects in both sexes on day 0.

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for an acute neurotoxicity study in rats (OPPTS 870.6200, OECD 424).

### 870.6200b Subchronic Neurotoxicity Screening Battery - Rat

In a subchronic neurotoxicity study (MRID 43294101), tetrachlorvinphos (99% a.i.; Lot #01-KMJ-012) was administered via the diet to 10 Sprague-Dawley Crl:CD®BR rats for 90 days at dose levels of 0, 200, 1000, or 5000 ppm. A Functional Operational battery (FOB) and motor activity were assessed at weeks -1, 0, 3, 7, and 12.

There were no deaths or clinical signs of toxicity. There were no measurement of cholinesterase activity, but cholinergic signs were not observed. Decreased body weight was observed throughout the study in males at 5000 ppm (8%-9%) and in females at 2000 ppm (8%-10%) and 5000 ppm (7%-13%). There were no indications of any dose-related effects during the home-cage, handling, open-field, sensory or neuromuscular observations. There were no significant dose-related differences between groups involving group mean motor activity counts. Brain weights and brain measurements (weight and morphometric) were comparable among the groups for both sexes, and there were no differences in histomorphological neurology findings between the control and 5000 ppm groups.

The NOAEL is 5000 ppm (250 mg/kg/day; standard conversion). The LOAEL was not identified.

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for a subchronic neurotoxicity study in rats (OPPTS 870.6200, OECD 424).

### 870.6300 Developmental Neurotoxicity - Rat

In a developmental neurotoxicity study (MRID 46660601), tetrachlorvinphos (99.6% a.i.; Lot #: NJ250RB08) in aqueous 1% (w/v) methylcellulose was administered via gavage (10 mL/kg) to pregnant Sprague-Dawley rats (25/dose) from gestation day (GD) 6 to lactation day (LD) 6 at doses of 0, 10, 50, or 200 mg/kg/day. Additionally, the $F_1$ pups were similarly dosed on postnatal days (PNDs) 7-21. Dams were allowed to deliver naturally and were sacrificed on LD 21. On PND 4, litters were standardized to 10 pups/litter; the remaining offspring and dams were sacrificed and subjected to a gross necropsy. Subsequently, 1 pup/sex/litter/group (at least 10 pups/sex/dose when available) were allocated to the following subsets: Subset 1, PND 21 brain weights and neurohistological evaluations; Subset 2, water maze and passive avoidance test; Subset 3, motor activity and auditory startle habituation; Subset 4, terminal brain weights and neurohistological evaluations; and Subset 5, standardize litter size to ten pups (5 male and 5 female) per litter on PND 4-21.

In dams, there were no treatment-related effects on mortality, clinical signs, body weight, body weight gain, feed consumption, FOB, or gross pathology. No treatment-related effects on reproductive parameters were observed. **The maternal LOAEL was not observed. The maternal NOAEL was 200 mg/kg/day (HDT).**

In offspring, there were no treatment-related effects on viability, litter observations, clinical signs, body weight, food consumption, FOB, motor activity, acoustic startle habituation, learning and memory (passive avoidance and water maze), gross pathology, or histopathology parameters.

At 200 mg/kg/day, decreases ($p \leq 0.05$) in body weight were noted in the males (↓5-8%) on PNDs 15 and 16 (pre-weaning) and PND 22 (post-weaning) and in the females (↓6%) on PND 29 (post-weaning). Body weight gains were decreased ($p \leq 0.05$) during pre-weaning at several intervals in the males (↓12-28%) and females (↓13-26%). Decreases ($p \leq 0.05$) in body weight gains during post-weaning were observed in the males on PNDs 21-22 (↓36%) and in the females on PNDs 21-22 and 22-29 (↓7-28%). Absolute brain weight was decreased ($p \leq 0.01$) by 8% in the males. This finding was judged to correlate with the treatment-related decreases ($p \leq 0.05$) in several microscopic linear brain measurements: (i) thickness of the striatum on PND 21 (↓4-5% both sexes) and PND 70 (↓7% males only); (ii) thickness of the corpus callosum on PND 70 (↓16-21% both sexes); (iii) thickness of the hippocampal gyrus on PND 70 (↓7-9% both sexes); and (iv) height of the cerebellum on PND 70 (↓7% males only). It is noted that on PND 21, decrease in single morphometric parameter was seen in both sexes with the small magnitude (4-5%) whereas on PND 70, decrease in multiple morphometric measurements were seen in both sexes with greater magnitude (7-21%) than that seen in PND 21.

No treatment related effects were noted in the ≤50 mg/kg/day $F_1$ offspring.

**The offspring LOAEL was 200 mg/kg/day, based on decreases in body weight, body weight gains and several morphometric linear brain measurements in both sexes, and decreased absolute brain weight in the males on PND 70. The offspring NOAEL was 50 mg/kg/day.**

This study is classified **as Acceptable/Guideline,** and it satisfies the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6; OECD 426) in the rat.

## A.4.8 Metabolism

### 870.7485 Metabolism – Rat

In a metabolism study (MRID 41988401), single oral doses of $^{14}C$-tetrachlorvinphos (97%; Lot # 2587-180; $^{14}C$ in the phenyl group) were administered *via* gavage to three groups of Sprague-Dawley rats (5/sex) at (A) 5 mg/kg, (B) 5 mg/kg following 14 consecutive doses of unlabeled test material, or (C) 250 mg/kg, and urine (0-8 hours, 8-24 hours, and at 24-hour intervals up to 120 hours post dose) and feces (at 24-hour intervals up to 120 hours post dose) were collected. At 120 hours post dose, the rats were sacrificed, and whole blood/plasma, heart, lungs, liver, kidney, spleen, gastrointestinal tract, brain, ovaries/testes, total skin, and samples of muscle, fat, and bone, and the remaining carcass were collected for analysis.

Most of the radioactivity was recovered in urine (46%-60%) and feces (38%-56%) within 48 hours post dose. The greatest activity in the urine was found in the 0-8 hour interval for both sexes following the single and repeat 5 mg/kg dose, whereas the greatest activity following the 250 mg/kg dose was found in the 8-24 hour interval. Following the single 250 mg/kg dose, males excreted a similar % (≈50%) of the dose *via* the urine and feces, whereas the females excreted the majority *via* the urine (70% vs 30%). Following the single 5 mg/kg dose, males excreted 60%



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*via* the urine and 40% via the feces, and females excreted equal amounts (≈50%) *via* the urine and feces. Following the 14-day dosing period, both sexes excreted approximately equal amounts (≈50%) *via* the urine and feces. Only minor amounts (<0.5%) of the radiolabel were recovered from tissues after 5 days, with the GI tract, whole blood, and lungs showing the highest concentrations. The major metabolite in urine was trichloromandelic acid (18%-26%), and the major metabolite in feces was trichlorophenylethanol (>13%). Since the oral LD50 for female rats is lower than the male LD50, it is noteworthy that males of all groups excreted more total label as trichloromandelic acid, a more completely metabolized form of TCVP, whereas the high-dose females tended to excrete more of the label as desmethyl TCVP (with the phosphate group still attached to the remainder of the molecule), a compound that could be derived from TCVP with only a single metabolic step.

The metabolism study is classified as Acceptable/Guideline, and it satisfies the guideline requirement for a metabolism study (OPPTS 870.7485, OECD 417) in rodents.

#### 870.7600 Dermal Penetration Study – Rat

In a dermal absorption study (MRID 42111501), male CD rats (28/group/time point) were exposed dermally to doses of 0.01, 0.1, 1 or 5 mg/cm$^2$ radiolableled tetrachlorvinphos (97% a.i.), with some of each dose group sacrificed at 0.5, 1, 2, 4, or 10 hours. Additionally, there was a group of animals, sacrificed at 72 hours, in which the skin was washed at 10 hours. The area of the dermal application was washed to recover unabsorbed tetrachlorvinphos. Then, the skin, urine, feces, and carcass were analyzed for percent of total tetrachlorvinphos applied. For the group sacrificed at 10 hours, 84 % of the total tetrachlorvinphos applied (0.1 mg/cm$^2$) was recovered in the wash, and 9.57 % was in the skin, urine, feces, and carcass. The percent absorption increased with duration of exposure and generally decreased with increasing dose. The actual quantity of tetrachlorvinphos absorbed increased with increasing dose.

This study is classified as **Acceptable/Guideline**, and it satisfies the guideline requirement (OCSPP 870.7600) for a dermal penetration study in the rat.

### A.4.9 Immunotoxicity

#### 870.7800

In an immunotoxicity study (MRID # 48794701), Tetrachlorvinphos [100.05%, lot #100113] was administered to Crl:CD-1(ICR) female mice (10/dose) via oral gavage at dose levels of 0, 75, 300, or 1200 mg/kg/day for 28 consecutive days. An additional group of 10 positive control females received cyclophosphamide 10 mg/kg/day via gavage for 28 days. On Day 25 a single intravenous (IV) dose of 0.25 mL/animal of sheep red blood cells (SRBC) 2x10$^8$ cells/animal was administered to all animals. During the study, clinical signs, morbidity and mortality, bodyweight, food consumption, water consumption were measured and evaluated. On Day 29, blood samples were collected from the orbital sinus under isoflurance anaesthesia. Animals were euthanized



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with carbon dioxide followed by exsanguination. All animals were subject to a complete necropsy examination. Spleen and thymus weights were recorded and immunotoxicity investigations by an Enzyme-linked immunosorbent assay (ELISA).

There were no treatment-related clinical signs and no unscheduled deaths. There were no treatment-related effects on body weights, food or water consumption. There were no treatment related necropsy findings. Absolute and relative mean thymus weight were statistically significantly lower ($p<0.05$) at 300 mg/kg/day group when compared with the vehicle control group. There were lower mean absolute thymus weight at 1200 mg/kg/day but it was not statistically significant; and there was no dose-dependent response in treated groups. Spleen weights in treated groups were not significantly different from the vehicle control group.

**For systemic toxicity, the NOAEL is 1200 mg/kg/day, the LOAEL was not established.**

When compare to the vehicle control group, the low and mid dose groups (75 and 300 mg/kg/day) had slightly higher anti-SRBC IgM levels, and the highest dose group (1200 mg/kg/day) had lower IgM levels. However, there were no statistically significant treatment-related effects on the specific anti-SRBC antibody response. High inter-individual variability was noted in all the treatment groups as well as in the control group. Evaluation of the individual animal data of this study did not show any trend or distribution that would demonstrate significant suppression of anti-SRBC IgM response. Animals in positive control group showed a statistically significant ($p< 0.05$) decrease of the anti-SRBC IgM response. This confirmed the ability of the test system to detect immuno-suppressive effects and confirmed the validity of the study design.

The NK cells activity assay was not performed. The toxicology database for tetrachlorvinphos does not reveal any evidence of treatment-related effects on the immune system. The overall weight of evidence suggests that this chemical does not directly target the immune system. Under HED guidance, a NK cells activity assay is not required at this time.

**For immunotoxicity, the NOAEL is 1200 mg/kg/day, tested above the limit dose; the LOAEL was not established.**

This immunotoxicity study is classified **acceptable/ guideline**, and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in mice.

## Special Studies

### Comparative Cholinesterase Studies

A series of studies (acute, repeat, gestational) was performed to investigate the effect of TCVP on brain and blood cholinesterase (ChE) activity and to determine the peak time of ChE

inhibition following both acute and repeated dosing in pre-weaning, young, maternal, and adult Sprague Dawley rats.

**Comparative Cholinesterase Assay - Repeat (11-days) Dose**:

In a comparative cholinesterase study (2012, MRID No.: 48773401), five groups of 10/sex of both 11 day old and young adult (~61 days) Crl:CD(SD) strain rats were dosed *via* gavage at dose levels of 0, 5, 10, 50 or 200 mg/kg/day of tetrachlorvinphos (TCVP) in methylcellulose. After 11 doses, the rats were sacrificed and assessed for red blood cell (RBC) and brain cholinesterase (ChE) activity.

*Systemic effects.* One female pup in the high dose group died after only two doses and its death was attributed to treatment. There was some decrease in body weight in this rat pup prior to death and the appearance was described as moderately dehydrated but no signs of typical ChE inhibition toxicity were reported. No other pups demonstrated clinical signs. There was an initial negative body weight gain in the adult males (days 1-2) but no clinical signs were evident in the adults.

**The LOAEL for systemic effects for both ages is 200 mg/kg/day, based on a single death of a female pup. The NOAEL is 50 mg/kg/day.**

*RBC ChE inhibition.* Adult males demonstrated a statistically significant reduction (13.3%) in RBC ChE level at 10 mg/kg/day. At 50 mg/kg/day, both male pups and adults had similar levels of inhibition (30% to 33%). At 200 mg/kg/day, the male pups were inhibited more (59.9%) than the male adults (36.3%). At 50 mg/kg/day, adult females demonstrated more inhibition (40.6%) than the female pups (19.2%) but at 200 mg/kg/day both female pups and adults had ~62% inhibition.

**The LOAEL for RBC ChE inhibition is 50 mg/kg/day for both sexes and both ages. The NOAEL is 10 mg/kg/day.**

*Brain ChE.* There was a dose-related decrease in brain ChE in adult females that was statistically significant at 10 mg/kg/day (↓12.2%), 50 mg/kg/day (↓42%), and 200 mg/kg/day (↓57.2%). Both sexes of pups displayed similar levels of brain ChE inhibition at 50 mg/kg/day (males ↓15.7%/females ↓18.7%) and 200 mg/kg/day (males ↓46.3%/females ↓45.1%), which were statistically significant. The adult males displayed statistically significant brain ChE inhibition at 50 mg/kg/day (↓14.9%) and 200 mg/kg/day (↓17.8%), although the magnitude of the response was similar at both dose levels.

**The LOAEL for brain ChE inhibition is 10 mg/kg/day, based on significant inhibition in adult females. The NOAEL is 5 mg/kg/day in adult females. The LOAEL for brain ChE inhibition is 50 mg/kg/day in male and female pups and in male adults. The NOAEL in male and female pups and in male adults is 10 mg/kg/day.**



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*Overall conclusion.* The main objective of this study was to determine if the pups are more sensitive than the adults to the cholinesterase inhibitory potential of TCVP. A comparison of the magnitude of cholinesterase inhibition in the brain and RBC compartments in the females shows the female pups with less inhibition (at 50 mg/kg/day) or a comparable amount of inhibition (at 200 mg/kg/day) as the female adults. For the males, a similar magnitude of inhibition was displayed in the pups and adults at 50 mg/kg/day, although the male pups displayed a greater % inhibition in both compartments at 200 mg/kg/day than the adult males. Based on assignment of the NOAEL and LOAEL, there was no demonstration for increased sensitivity of the pups relative to the adults for either RBC or brain ChE. Although the magnitude of brain inhibition in the male pups was greater than in the male adults, this occurred only at the 200 mg/kg/day dose level. The benchmark dose analysis of the brain cholinesterase data does not show the male pups to be more sensitive.

A benchmark dose analysis of the repeat dose cholinesterase data (RBC and brain) was performed that provides both the $BMD_{10}$ and $BMDL_{10}$ of adults and PND11 pups.

| **$BMD_{10}$s and $BMDL_{10}$s for Adult Rat and PND 11 Pup Cholinesterase** | | | | |
|---|---|---|---|---|
| | **RBC $BMD_{10}$** | **RBC $BMDL_{10}$** | **Brain $BMD_{10}$** | **Brain $BMDL_{10}$** |
| Adult males | 7.7178 | 3.5942 | 33.803 | 24.4489 |
| Adult females | 8.6762 | 6.1335 | 7.1764 | 5.4980 |
| PND 11 males | 20.4688 | 15.9719 | 33.4825 | 26.5707 |
| PND 11 females | 20.5608 | 13.1692 | 24.2224 | 18.9412 |

***Classification:*** The classification of this repeat dose *in vivo* comparative cholinesterase inhibition study is Acceptable/Non-Guideline. It does not satisfy a guideline requirement. It satisfies the generic data call-in requirement for TCVP for a comparative cholinesterase study in adult rats versus postnatal day (PND) 11 rat pups.

**Comparative Cholinesterase Assay - Acute Dose**

In an acute comparative cholinesterase study (MRID 48773401a), TCVP (98.99% a.i.; Batch # TX100405)] was administered to 10 Crl:CD (SD) adult rats/sex/dose, 10 Crl:CD (SD) postnatal day (PND) 11 pups/sex/dose, and 10 Crl:CD(SD) PND 21 pups/sex/dose once *via* gavage (10 mL/kg) at dose levels of 0 (1% w/v aqueous methylcellulose), 10, 50, 150, or 300 mg/kg. Viability, clinical signs, body weights, and brain weights were evaluated. Approximately three hours post dose, red blood cell (RBC) and brain acetylcholinesterase (AChE) levels were determined.

There were no treatment-related deaths. Treatment-related clinical signs included soft or liquid feces in several adult males at 150 mg/kg and 300 mg/kg, decreased motor activity in PND 21 males and females at 150 mg/kg and 300 mg/kg, and urine-stained abdominal fur in PND 21 rats at 300 mg/kg. There were no clinical signs in the PND 11 pups or adult females.

Cholinesterase inhibition was displayed in both compartments in all age groups at all dose levels, with one exception. The magnitude of the response in the adult female rats (RBC and brain) was lower than in the adult male rats and in both sexes of PND 11 and PND 21 pups.

For both compartments, the magnitude of the response was comparable among the age groups and similar between the sexes, with the exception of the adult female rats. *All groups showed a similar response in both the RBC and brain cholinesterase compartments at each dose level.*

**The NOAEL for adult rats (both sexes) for RBC and brain cholinesterase inhibition following an acute oral dose was not determined. The LOAEL for adult rats is 10 mg/kg.**

**The NOAEL for PND 21 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 21 pups is 10 mg/kg.**

**The NOAEL for PND 11 pups could not be determined, based on RBC and brain cholinesterase inhibition at all dose levels following acute oral exposure. The LOAEL for PND 11 pups is 10 mg/kg.**

This comparative study of RBC and brain cholinesterase activities following acute oral treatment with TCVP in adult and neonatal (PND 11 and PND 21) rats is classified **Acceptable/Non-guideline.** It does not satisfy any guideline requirement; however, it does satisfy the data requirement for TCVP for an acute comparative cholinesterase activity between adult and young rats.

**COMMENT**: This acute exposure comparative cholinesterase study final report was embedded within the repeat dose comparative cholinesterase study report (MRID 48773401); it should have been submitted as a separate study report and been given a unique MRID #. The results of the Benchmark dose analysis for the acute study are provided below.

| TCVP/Study | Sex/Age | Compartment | BMD Results (mg/kg) | |
|---|---|---|---|---|
| | | | $BMD_{10}$ | $BMDL_{10}$ |
| MRID 48773401a Acute CCA | Male PND11 | Brain | 5.1 | 4.5 |
| | Female PND11 | Brain | 5.9 | 4.8 |
| MRID 48773401a Acute CCA | Male PND11 | RBC | 5.0 | 4.1 |
| | Female PND11 | RBC | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | Male PND21 | Brain | 3.5 | 3.2 |
| | Female PND21 | Brain | 5.3 | 3.7 |
| MRID 48773401a Acute CCA | Male PND21 | RBC | 3.2 | 2.8 |
| | Female PND21 | RBC | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Male Adult | Brain | 7.4 | 5.6 |
| | Female Adult | Brain | 11.6 | 9.8 |
| MRID 48773401a | Male Adult | RBC | 6.5 | 3.6 |

| | | | | |
|---|---|---|---|---|
| Acute CCA | Female Adult | RBC | 14.9 | 11.2 |

**Comparative Cholinesterase Assay - Gestational Exposure**

In a maternal and fetal exposure study (2010, MRID 48291101), tetrachlorvinphos (TCVP) (purity 99.6%, Lot No. NJ250RB08) dissolved in 1% aqueous (w/v) methylcellulose was administered to pregnant female Crl:CD(SD)IGS BR VAF/Plus rats via gavage once daily on days 6 through 21 of gestation at doses of 0, 75, 150 or 300 mg/kg/day. On gestation day 21 (GD 21), within 2 hr of the last dose, whole blood samples and brains were collected from the dams for cholinesterase (ChE) assessment. Dams were Caesarean-sectioned and pooled fetal blood samples and brains were collected for ChE assessment.

***Maternal Systemic and Litter Effects:*** All dams survived until scheduled sacrifice and no adverse clinical observations were reported. No Caesarean-sectioning or litter parameters were affected. Body weight *gains* and food consumption in dams were reduced in the 150 and 300 mg/kg/day groups. No gross lesions were observed during necropsy of the dams. There were no fetal gross external alterations and fetal body weights, brain absolute and relative weights were comparable among the dose groups. Since the main purpose of this study was to assess differential sensitivity between the dams and the fetuses, no assignment of a NOAEL and LOAEL for maternal systemic and litter effects is being made.

***RBC ChE***: Neither the dams nor the fetuses demonstrated RBC ChE inhibition. In dams the values were 5.1%, 15% and 3% lower than the control for the low, mid and high doses, respectively. Interpretation of the fetal RBC data was confounded because only 1 or two samples were available and no sample was available for the mid dose group. *The RBC ChE data are considered unacceptable because the repeat dosing study (2012, 48773401) conducted in the same laboratory in the same strain of rat was clearly able to demonstrate RBC ChE inhibition at 50 and 200 mg/kg/day in females. There was no way to compare adult and fetal RBC ChE.*

***Plasma ChE***. Plasma ChE inhibition in dams was dose dependent being 62%, 71% and 77% for the low, mid and high dose groups, respectively. Fetal plasma ChE values were 22%, 18.5% and 20.8% less than the control for the low, mid and high dose groups, respectively. The lack of a dose response raises the question as to whether these lower values are actually inhibition. However, there is no indication that the fetuses are more sensitive than the dams for this compartment.

***Brain ChE.*** Brain ChE inhibition was also dose dependent in dams; *i.e.*, 31%, 44% and 67% for the low, mid and high doses, respectively. Fetal brain ChE values were 10%, 20.9% and 20.8% lower than the controls for the low, mid and high dose groups, respectively. Similar to the plasma ChE data, there is no dose response to support a conclusion that these lower values are actually inhibition. However, there is no indication that the fetal brain ChE is more sensitive to inhibition by TCVP than the dams.

This *in vivo* comparative ChE study is classified as **Acceptable/non-guideline**. The study does not satisfy a guideline requirement. It satisfies a data call-in-requirement for TCVP for a gestational comparative ChE study in maternal rats versus fetal rats, although it is to be noted that the dose levels selected are way too high. However, from the data available, no increase in sensitivity was evident. RBC ChE inhibition was not demonstrated in the dams or fetuses (no data), and the flat dose response curves for the brain ChE in both pups and adults confound the interpretation of the study. However, no additional gestational CCA study is being requested at this time because there is no indication that the fetuses were more affected than the dams.

**Comparative Cholinesterase Assay - Acute Exposure**

In an acute relative cholinesterase (ChE) sensitivity study (2010, MRID 48294601), tetrachlorvinphos (TCVP) (purity 99.6%, Lot No. NJ250RB08) was administered at doses of 0, 75, 150 or 300 mg/kg body weight dissolved in 1% aqueous (w/v) methylcellulose to Crl:CD(SD)IGS BR VAF/Plus strain young adult (about 42 days old) and to postnatal day (PND) 11 and 21 neonatal rats via a single oral (gavage) dose. Four rats/sex/dose were sacrificed on pretest and at 1, 2, 3, 4, 8 and 24 hours after dosing.

***Systemic effects.*** All pups and all adult rats groups survived. There were no adverse clinical or necropsy observations related to the TCVP administration, and no effects on body or brain weights were reported. Since this is a short term study primarily designed to assess for comparative sensitivity to ChE inhibition, no NOAEL or LOAEL for systemic effects will be assigned.

***General comments on ChE assessment.*** Only four rats/sex were available for assessment at each of the seven assessment times. Many of the RBC and plasma ChE assessments were made on only 0 (no sample available), 1, 2, or 3 samples because of loss of sample. In addition, duplicate samples that did not replicate contributed to the low number of sample to provide a meaningful mean. Brain ChE also appeared to be affected by the low number of samples. The results for all three enzyme sources indicated that there was inhibition at all doses but there was poor dose response with the degree of apparent inhibition at the higher doses often less that at the low dose of 75 mg/kg/day. There was also a lack of temporal concordance with high apparent inhibition at one time, a much lower degree at the following time and back to the higher level at the next time point. Another problem is that there was more or similar apparent inhibition at the low dose of 75mg/kg in this acute study than there was in the repeat dosing studies (2012, MRID 48773401, eleven daily doses) at 200 mg/kg/day and in the gestational study (2010, MRID 48291101, fifteen daily doses) at 150 mg/kg/day. Also, the repeat dosing study clearly indicated that there was no increase in sensitivity of the pups relative to the adults with regard to potential inhibition by TCVP. In this acute study, there were several comparisons among the PND11, PND21 and adults that suggested the pups were more sensitive.

Overall, there is little confidence in the data mainly because of the lack of clear dose and temporal responses.

***Benchmark Dose (BMD) modeling.*** BMD modeling was performed but could not be done with the RBC data or for the PND11 brain data because of too few samples and/or the data would not otherwise fit the models. BMD modeling for the brain data (for the three hour assessment time) indicated that for males, the adults may be slightly more sensitive than the PND 21 pups but the females were considered similar with respect to the $BMD_{10}$ and $BMDL_{10}$.

| **TCVP/Study** | **Sex/Age** | **Compartment** | **BMD Results** (mg/kg/day) | |
|---|---|---|---|---|
| | | | **$BMD_{10}$** | **$BMDL_{10}$** |
| MRID 48294601 Acute CCA | Adult male | Brain | 6.76716 | 5.02249 |
| MRID 48294601 Acute CCA | Adult female | Brain | 11.2932 | 4.55107 |
| MRID 48294601 Acute CCA | Male pup PND 21 | RBC | 16.8647 | 9.71265 |
| MRID 48294601 Acute CCA | Female pup PND 21 | Brain | 9.80073 | 4.6942 |
| MRID 48294601 Acute CCA | Male pup PND 21 | Brain | 11.246 | 6.76389 |

This study is classified as A**cceptable/Non-Guideline.** The study does not satisfy a guideline requirement. It satisfies a data call-in-requirement for TCVP for an acute comparative ChE study in adult, PND 21, and PND 11 pups, although there is too much variability in the data to make meaningful comparisons for sensitivity for RBC. Brain ChE data also had problems with variability and dose response to compare for sensitivity. However, from the data available, there is no conclusive evidence of increased sensitivity. No additional acute CCA study is being requested at this time because there is no indication that the young animal was more affected than the adult. NOTE: An additional acute comparative cholinesterase study (MRID 48773401a) was located and is discussed above.

## Appendix B. Results for BMD/BMDL modeling for TCVP

### B.1. Summary of OPP's ChE Policy & Use of BMD Modeling

OPP's AChE policy (USEPA, 2000[1]) describes the manner in which AChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or cholinesterase (ChE) inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung etc) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and RBC) ChE. Blood measures do not represent the target tissue, per se, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-ChE (BuChE). Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.

Refinements to OPP's use of AChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often the decreasing exponential empirical model has been used.

OPP does not have a defined BMR for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the $BMD_{10}$ is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the $BMD_{10}$.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by the Office of Research and Development (ORD) on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity in the brain compartment and is a response level close to the background brain AChE level. With respect to biological considerations, a change in 10% brain AChE inhibition is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC AChE inhibition, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC AChE inhibition but BMRs up to 20% could be considered on a case by case basis as long as such PODs are protective for brain AChE inhibition, potential peripheral inhibition, and clinical signs of neurotoxicity.

## B.2. Summary Tables of Benchmark Dose (BMD) Analyses

BMD analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using an exponential model for continuous data (Bever and Holman, D435480, 9/1/2016). The data selected for evaluation consisted of decreased brain and red blood cell (RBC) cholinesterase (AChE) activities from rats in an acute comparative cholinesterase assay (CCA; MRID 48773401a). The results of the acute dosing BMD analyses are summarized below in Table B.1.

**Table B.1. Results of BMD Modeling (mg/kg) for Brain and RBC ChE Data on TCVP, Acute Oral Dosing Study in Rats.**

| Study | Age Sex | Brain $BMD_{10}$ | Brain $BMDL_{10}$ | RBC $BMD_{10}$ | RBC $BMDL_{10}$ |
|---|---|---|---|---|---|
| MRID 48773401a Acute CCA | PND 11 Male | 5.1 | 4.5 | 5.0 | 4.1 |
| MRID 48773401a Acute CCA | PND 11 Female | 5.9 | 4.8 | 3.4 | 2.8 |
| MRID 48773401a Acute CCA | PND 21 Male | 3.5 | 3.2 | 3.2 | 2.8 |

| | | | | | |
|---|---|---|---|---|---|
| MRID 48773401a Acute CCA | PND 21 Female | 5.3 [a] | 3.7 | 4.6 | 2.8 |
| MRID 48773401a Acute CCA | Adult Male | 7.4 | 5.6 | 6.5 | 3.6 |
| MRID 48773401a Acute CCA | Adult Female | 11.6 [a] | 9.8 | 14.9 | 11.2 |

CCA = Comparative Cholinesterase Assay

[a]Although the model chosen resulted in program warning that "the model may not adequately describe the data", fit was considered adequate based on similarity to values from other data sets, plausibility after considering empirical data (ground-truthing), and visual assessment of the fit.

Previously, Benchmark Dose (BMD) analyses were performed with EPA's Benchmark Dose Software (Version 2.4) using an exponential model for continuous data [2]. The Hill model was also performed for some data sets, but did not result in the best fit for the data. The data selected for evaluation consisted of decreased brain and red blood cell (RBC) cholinesterase (ChE) activities. Data were analyzed from a 21-day oral toxicity study (MRID 45570601), a 13-week subchronic oral toxicity study (MRID 43371201), a 2 year chronic oral toxicity study (MRID 42980901); a gestational comparative cholinesterase assay (MRID 48291101); and a 28-day inhalation toxicity study (MRID 48803501). The results of the repeated oral and inhalation dosing BMD analyses are summarized below in Table B.2. Good model fit ($p>0.1$) was obtained for the majority of the analyses, with any exceptions being noted.



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| Table B.2. Results of BMD Exponential Modeling for Brain and RBC ChE Data on TCVP, Repeated Oral Dosing Studies in Rats, Ranging in Duration from 21 days to 2 years. | | | | |
|---|---|---|---|---|
| **TCVP Study** | **Age/Sex** | **Compartment** | **BMD Results** | |
| | | | **$BMD_{10}$** | **$BMDL_{10}$** |
| MRID 43371201 13W Oral – 13 Weeks | Adult Male | Brain | No dose response (analysis not performed) | |
| | Adult Female | Brain | No dose response | |
| | Adult Male | RBC | 61.6 mg/kg/day | 26.3 mg/kg/day |
| | Adult Female | RBC | 10.5 mg/kg/day | 8.0 mg/kg/day |
| MRID 42980901 Chronic Oral Tox – 364, 539, and 721 Days | Adult Female | RBC | No dose-response effect was observed at 364, 539, or 721 days | |
| MRID 45570601 21D Oral Tox – 21 Days | Adult Female | Brain | 14.7 mg/kg/day | 12.2 mg/kg/day |
| | | RBC | 9.9 mg/kg/day | 6.7 mg/kg/day |
| MRID 48803501 28D Inhalation – 28 Days | Adult Male | RBC | 0.122 mg/L | 0.022 mg/L |
| | Adult Female | RBC | 0.394 mg/L | 0.050 mg/L |

[1] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of the Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.
[2] J. Bever. Tetrachlorvinphos: Benchmark Dose Analysis of Subchronic and Chronic Studies to Support Derivation of Points of Departure. 5/20/2014. TXR # 0056970. D420286.

## Appendix C. Methodologies for HEC Calculations

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (e.g., systemic vs. portal-of-entry) and the pharmacokinetic (PK) **but not pharmacodynamic** (PD) differences between animals and humans. Based on the EPA's RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (e.g., systemic vs. portal-of-entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (e.g., acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid. These assumptions, in turn, vary depending on the type of toxicity observed. Thus the derivation of a HEC for inhaled gases is described by the following equation:

$$HEC = POD_{study} * \frac{D_{\text{animal exposure (hrs / day)}}}{D_{\text{human exposure (hrs / day)}}} * \frac{W_{\text{animal exposure (days / wk)}}}{W_{\text{human exposure (days / wk)}}} * RGDR$$

Where:
$POD_{study}$: Point of departure identified in the critical toxicology study
$D_{\text{animal exposure}}$: Duration of animal exposure (hrs/day; days/wk)
$D_{\text{anticipated exposure}}$: Anticipated human duration of exposure (hrs/day; days/wk)
RGDR: Regional Gas Dose Ratio

Calculations used to estimate the inhalation risk to humans from aerosols are dependent not on the RGDR as for gases, but on the regional deposited dose ratio (RDDR). Inhalation studies using aerosols characterize particulate exposure by defining the particulate diameter (mass median aerodynamic diameter [MMAD]) and the geometric standard deviation ($\sigma_g$), which is then used to determine the RDDR. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the rth region or target tissue.

$$RDDR_r = \frac{(RDD_r/\text{Normalizing Factor})_A}{(RDD_r/\text{Normalizing Factor})_H}$$

As with calculations for gases, the r regions and potential target tissues are the three respiratory regions (ET, TB, PU). The RDDR is easily calculated by using a software program designed specifically for computing the RDDR from the MMAD and $\sigma_g$ defined from an aerosol inhalation study. The values for the species-specific parameters used to calculate the RDDR are



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provided in the EPA document "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry."

**Regional Deposited Dose Ratio (RDDR) for TCVP**

MMAD = 2.57
Sigma g = 3.79

| SPECIES | Body Weight (g) | Minute Ventilation (VE, ml) |
|---|---|---|
| rat | 267 | 189.8 |
| human | 70000 | 13800.0 |

| | Extrarespiratory BW (g) | deposited fraction |
|---|---|---|
| rat | 267 | 0.460 |
| human | 70000 | 0.657 |
| RATIO | 0.004 | 0.700 |

RDDR = $(VE/BW)_{animal}/(VE/BW)_{human}$ * deposited $fraction_{animal}$/deposited $fraction_{human}$
= $(189.8/267)_{animal}/(13800/70000)_{human}$ * 0.460/0.657
= 2.525

The magnitude of the UFs applied is dependent on the methodology used to calculate risk. The RfC methodology takes into consideration the PK differences **but not the PD differences**. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology is customarily 30X.

***C.1. HEC Calculations for Residential Exposure:***

*Assume residents will be exposed for 24 hrs/day and 7 days/week:*

*HEC = $NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR*

*Residential Bystander HEC = 0.022 mg/L * (6/24) * (5/7) * 2.525 = 0.0099 mg/L*
*Residential Handler Outdoor HEC = 0.022 mg/L * 2.525 = 0.0555 mg/L*



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| Table C.1.1. HEC Array for Residential Handler Risk Assessment. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 8 | 5 | 5 | 2.525 | 0.0555 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Table C.1.2. HEC Array for Residential Bystander Risk Assessment. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 24 | 5 | 7 | 2.525 | 0.099 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Key for Array Tables | |
|---|---|
| *LOAEL*: Lowest-observed adverse-effect level | *RRDR*: Regional Deposited Dose Ratio |
| *NOAEL*: No-observed adverse-effect level | *HEC*: Human-Equivalent Concentration |
| *Da*: Daily animal exposure (hrs/day) | *inter*: Interspecies extrapolation UF |
| *Dh*: Anticipated daily human exposure (hrs/day) | *intra*: Intraspecies variation UF |
| *Wa*: Weekly animal exposure (days/week) | *UF*: Other UF(s) |
| *Wh*: Anticipated weekly human exposure (days/week) | *ER:* Extra-respiratory effects |

***Route-to-Route Extrapolation***

*More information and details in: Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/98.*

*HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes. An activity factor is used to account for increased exposure resulting from increased respiration.*

*Using the HEC calculated (based on an increase in RBC cholinesterase inhibition in both sexes), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:*

*HED (mg/kg/day) = Dose (systemic HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg*

*Where:*

*A = absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route.*

*CF = conversion factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of J. Whalen and H. Pettigrew, 10/10/98).*

*D = duration; duration of daily animal or human exposure (hours).*

*AF = activity factor; animal default is 1. For humans the value varies with ventilation*

**11.8 L/hr/kg is the typical breathing rate assumed for humans.*

*Therefore, the residential HED for TCVP is calculated as follows:*

***Residential Handler HED:*** *(0.056 mg/L) x 11.8 L/hr/kg x 2 hr x 1 = 1.31 mg/kg/day*

***C.2. HEC Calculations Occupational Exposure:***

*Assume workers will be exposed for 8 hrs/day and 5 days/week:*

*HEC = $NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR*

Occupational - HEC = 0.022mg/L * (6/8) * (5/5) * 2.525 = 0.0416 mg/L.

**Table C.1.3. HEC Array for Occupational Risk Assessment.**

| Relevant Study | | $BMDL_{10}$ (mg/L) | $BMD_{10}$ (mg/L) | Da | Dh | Wa | Wh | RDDR | HEC (mg/L) | Inter | intra | UF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Short-& Intermediate-Term Exposure | | | | | | | | | | | | |
| Inhalation – Rat (MRID 48803501) 28-day | ER | 0.022 | 0.122 | 6 | 8 | 5 | 5 | 2.525 | 0.0416 | 3 | 10 | NA |
| Long-Term Exposure: Not appropriate for TCVP. | | | | | | | | | | | | |

| Key for Array Tables | |
|---|---|
| *LOAEL*: Lowest-observed adverse-effect level | *RRDR*: Regional Deposited Dose Ratio |
| *NOAEL*: No-observed adverse-effect level | *HEC*: Human-Equivalent Concentration |
| *Da*: Daily animal exposure (hrs/day) | *inter*: Interspecies extrapolation UF |
| *Dh*: Anticipated daily human exposure (hrs/day) | *intra*: Intraspecies variation UF |
| *Wa*: Weekly animal exposure (days/week) | *UF*: Other UF(s) |
| *Wh*: Anticipated weekly human exposure (days/week) | *ER:* Extra-respiratory effects |

**Route-to-Route Extrapolation**

More information and details in: Memo, "Route-to-Route Extrapolations" J. Whalen and H. Pettigrew, 10/10/98.

HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral-equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes. An activity factor is used to account for increased exposure resulting from increased respiration.

Using the HEC calculated (based on an increase in RBC cholinesterase inhibition in both sexes), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:

HED (mg/kg/day) = Dose (systemic HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) x AF = mg/kg

Where:

| | | |
|---|---|---|
| A | = | absorption; ratio of deposition and absorption in respiratory tract compared to absorption by the oral route. |
| CF | = | conversion factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (Table 1 of J. Whalen and H. Pettigrew, 10/10/98). |
| D | = | duration; duration of daily animal or human exposure (hours). |
| AF | = | activity factor; animal default is 1. For humans, the value varies with ventilation rates |

Therefore, the occupational HED for TCVP is calculated as follows:

**Occupational Handler HED:** 0.042 mg/L x 11.8 L/hr/kg x 1.0 x 8 hr = 3.94 mg/kg/day

Based on the current TCVP label, HED believes exposures can be short- (1-30) or intermediate- (1 to 6 months) term in duration. Long-term exposures are not anticipated for TCVP based on proposed labeled uses. For the short- and intermediate-term scenarios, inhalation data from the 28-day inhalation rodent study was most appropriate for determining HECs. In the RfC methodology, different HECs may be calculated for the same experimental NOAEL due to the following:

1. Different algorithms are used to derive HECs for systemic versus portal-of-entry effects. Typically, HECs are calculated separately for systemic versus portal-of-entry effect. For TCVP, extra-respiratory effects were observed and, therefore, only extra-respiratory HECs were derived.

Time adjustments are traditionally needed for non-occupational (bystander) versus occupational exposure scenarios. Traditionally, HECs for non-occupational exposure are based on the number of hours an individual may be at home. Therefore, the most conservative estimate of hours spent at home would be 24 hours/day and 7 days/week. In comparison, the average workweek for an occupational worker is 8 hours/day and 5 days/week. The HEC array table reflects the time adjustment in the calculations.



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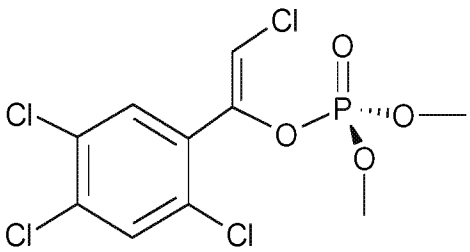
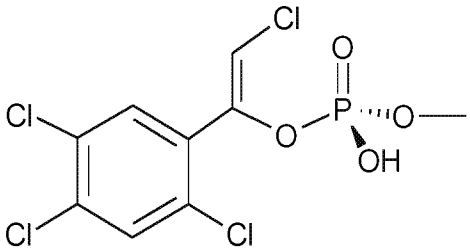
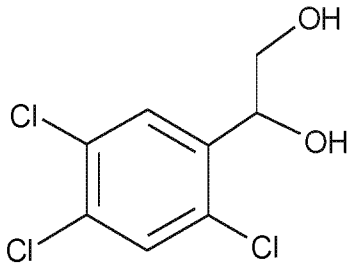
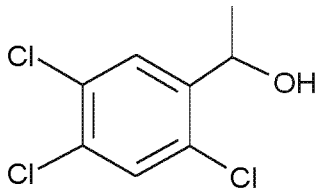
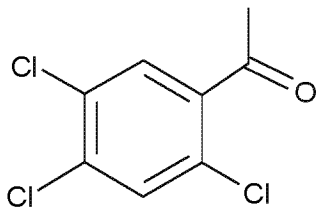
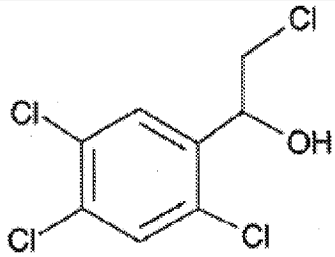
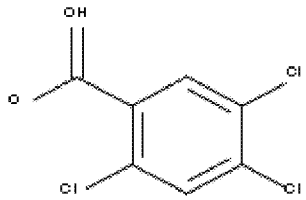
## Appendix D. Physical/Chemical Properties for Tetrachlorvinphos

| Table D.1 Physicochemical Properties of the Technical Grade Test Compound: Tetrachlorvinphos | | |
|---|---|---|
| Parameter | Value | Reference [1] |
| Melting point/range | 94.5 °C | (MRID 41222503) |
| pH | 5.5; 1% solution | (MRID 41222503) |
| Density | 0.83 g/mL | (MRID 41222503) |
| Water solubility | (25°C) 11.6 g/L | (MRID 41222503) |
| Solvent solubility | (mg/100mg at 25°C)<br>chloroform 80<br>methanol 21<br>acetone 44<br>hexane 0.8<br>toluene 28 | (MRID 41222503) |
| Vapor pressure | (25°C) 2.6 x $10^{-7}$ mm Hg | (MRID 41222503) |
| Dissociation constant, $pK_a$ | non-ionizable | (MRID 41222503) |
| Octanol/water partition coefficient, Log($K_{OW}$) | 3350 average $K_{OW}$ at 25 °C | (MRID 41222503) |
| UV/visible absorption spectrum | Not available | |

[1] Cited reference was reviewed under CB No. 7468, 4/3/91, R. Perfetti.

## Appendix E. TCVP and Metabolites

| Chemical Name | Structure | Physical/Chemical Properties[1] |
|---|---|---|
| **Tetrachlorvinphos**<br><br>IUPAC: (*Z*)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate<br><br>CAS: (*1Z*)-2-chloro-1-(2,4,5-trichlorophenyl)ethenyl dimethyl phosphate<br><br>CAS Reg. No. 22248-79-9<br><br>COP(=O)(OC)OC(=CCl)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 365.96 g/mol<br>VP: 2.6E-07 torr<br>Solubility: 11.6 mg/L<br>Log Kow: 3.53<br>Koc: 520-1100 L/$kg_{oc}$ |
| **Des-O-methyl tetrachlorvinphos**<br><br>IUPAC: (*Z*)-2-chloro-1-(2,4,5-trichlorophenyl)vinyl methyl phosphate<br><br>CAS: (*1Z*)-2-chloro-1-(2,4,5-trichlorophenyl)ethenyl methyl phosphate<br><br>COP(=O)(O)OC(=CCl)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 351.94 g/mol<br>VP: 4.27E-08 torr<br>Solubility: 3.768 mg/L<br>Log Kow: 3.75<br>Koc: 702-827 L/$kg_{oc}$ |
| **1-(2,4,5-trichlorophenyl)ethanediol**<br><br>C(O)(CO)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 241.5 g/mol<br>VP: 4.37E-06 torr<br>Solubility: 250 mg/L<br>Log Kow: 2.37<br>Koc: 29-36 L/$kg_{oc}$ |
| **TCPEol (SD 15509, AA849)**<br><br>1-(2,4,5-trichlorophenyl)ethanol<br>1-(2,4,5-trichlorophenyl)ethan-1-ol<br><br>CC(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 225.5 g/mol<br>VP: 2.37E-04 torr<br>Solubility: 123 mg/L<br>Log Kow: 3.43<br>Koc: 319-359 L/$kg_{oc}$ |
| **TCPEone (CO300)**<br><br>2,4,5-trichloroacetophenone<br><br>CC(=O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 223.5 g/mol<br>VP: 6.32E-03 torr<br>Solubility: 27.4 mg/L<br>Log Kow: 3.61<br>Koc: 492-1,828 L/$kg_{oc}$ |

| Chemical Name | Structure | Physical/Chemical Properties[1] |
|---|---|---|
| **TCCEol (SD15125, AA576)**<br><br>l-(2,4,5-trichlorophenyl)-2-chloroethanol<br><br>C(Cl)C(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 260 g/mol<br>VP: 2.11E-05 torr<br>Solubility: 250 mg/L<br>Log Kow: 3.68<br>Koc: 494-608 L/$kg_{oc}$ |
| **TCBA (SD 15917)**<br><br>2,4,5-Trichlorobenzoic acid<br><br>C(=O)(O)c1cc(Cl)c(Cl)cc1Cl |  | Molecular weight: 225.5 g/mol<br>VP: 5.52E-04 torr<br>Solubility: 35.3 mg/L<br>Log Kow: 3.47<br>Koc: 157-166 L/$kg_{oc}$ |

1. Physical and chemical properties for degradates obtained through EPISuite 4.11.

## Appendix F. International MRLs and U.S. Tolerances

| Table F.1. Tetrachlorvinphos: Summary of U.S. and International Tolerances and Maximum Residue Limits. | | | | |
|---|---|---|---|---|
| Commodity | U.S. Tolerances, 40 CFR §180.252 [1] | | Codex MRL | Canada's MRL [2] |
| | Established U.S. Tolerance, ppm | Reassessed U.S. Tolerance, ppm | | |
| Milk, fat (reflecting negligible residues in whole milk) | 0.5 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | milk: 0.1 (of which not more than 0.04 ppm is tetrachlorvinphos *per se*) | None | None |
| Cattle and Hog, Fat | Fat of cattle and hog: 0.2 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | Fat of cattle and hog: 1.0 (of which not more than 0.8 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Muscle | meat of cattle and hog: 2.0 (of which not more than 2.0 ppm is tetrachlorvinphos *per se*) | meat of cattle and hog: 0.3 (of which not more than 0.2 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Kidney | kidney of cattle and hog: 1.0 (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | meat byproducts of cattle and hog : 1.0 (of which no more than 0.6 ppm is tetrachlorvinphos *per se*) | None | 1.5 [3] |
| Cattle and Hog, Liver | liver of cattle and hog: 0.5 (of which no more than 0.05 ppm is tetrachlorvinphos *per se*) | | None | 1.5 [3] |

| Table F.1. Tetrachlorvinphos: Summary of U.S. and International Tolerances and Maximum Residue Limits. | | | | |
|---|---|---|---|---|
| Commodity | U.S. Tolerances, 40 CFR §180.252 [1] | | Codex MRL | Canada's MRL [2] |
| | Established U.S. Tolerance, ppm | Reassessed U.S. Tolerance, ppm | | |
| Cattle and Hog, Meat byproducts | meat byproducts, except kidney and liver of cattle and hog: 1.0 | | None | 1.5 [3] |
| Eggs | 0.2 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | 0.3 (of which not more than 0.03 ppm is tetrachlorvinphos *per se*) | None | None |
| Poultry, muscle | meat of poultry: 3.0 (of which not more than 3.0 ppm is tetrachlorvinphos *per se*) | meat of poultry: 0.4 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, liver | 2.0 (of which not more than 0.05 ppm is tetrachlorvinphos *per se*) | meat byproducts of poultry: 20 (of which not more than 6.0 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, meat byproducts | meat byproducts, except liver, of poultry: 2.0 | meat byproducts of poultry: 20 (of which not more than 6.0 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Poultry, fat | 7.0 (of which not more than 7.0 ppm is tetrachlorvinphos *per se*) | 1.4 (of which not more than 0.1 ppm is tetrachlorvinphos *per se*) | None | 0.75 [4] |
| Apples | None | None | None | 10 |
| Grapes | None | None | None | 10 |

## Appendix G. Summary of Residential Handler Non-Cancer Exposures and Risks

| Table G.1. Residential Handler Non-cancer Dermal and Inhalation Dose Assuming a Liquid or Dust Formulation for Pet Collars. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal Dose (mg/kg/day)[3] | Inhalation Dose (mg/kg/day)[4] |
| Assume Liquid Formulation -- Use of Spot-On Exposure Data (based on 2012 Residential SOPs) | | | | | | | |
| Application of TCVP Collars | 2596-49: Cat | 120 | Negligible | 0.0036: 11 gram collar | 2 animals treated per day | 0.0012 | Negligible |
| | 2596-50, 62: Dog | | | 0.0061: 19 gram collar | | 0.0020 | |
| | | | | 0.010: 32 gram collar | | 0.0034 | |
| | 2596-63: Cat | | | 0.0048: 15 gram collar | | 0.0016 | |
| | | | | 0.0055: 17 gram collar | | 0.0018 | |
| | 2596-83: Cat | | | 0.0039: 12 gram collar | | 0.0013 | |
| | | | | 0.0080: 25 gram collar | | 0.0027 | |
| | 2596-84: Dog | | | 0.0061: 19 gram collar | | 0.0021 | |
| | | | | 0.010: 32 gram collar | | 0.0034 | |
| | 2596-139: Cat | | | 0.0032: 10 gram collar | | 0.0011 | |
| | 2596-139: Dog | | | 0.016: 50 gram collar | | 0.0054 | |
| | 11556-164: Dog | | | 0.0072: 24 gram collar | | 0.0024 | |
| | 11556-165: | | | 0.0045: | | 0.0015 | |

| Table G.1. Residential Handler Non-cancer Dermal and Inhalation Dose Assuming a Liquid or Dust Formulation for Pet Collars. | | | | | | | |
|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal Dose (mg/kg/day)[3] | Inhalation Dose (mg/kg/day)[4] |
| | Cat | | | 15 gram collar | | | |
| **Assume Dust Formulation -- Use of TCVP Dust Applicator Exposure Data (MRID 45519601)** | | | | | | | |
| Application of TCVP Collars | 2596-49: Cat | 1,700 | 3.1 | 0.0036: 11 gram collar | 2 animals treated per day | 0.017 | 0.00033 |
| | 2596-50, 62: Dog | | | 0.0061: 19 gram collar | | 0.029 | 0.00055 |
| | | | | 0.010: 32 gram collar | | 0.049 | 0.00092 |
| | 2596-63: Cat | | | 0.0048: 15 gram collar | | 0.023 | 0.00043 |
| | | | | 0.0055: 17 gram collar | | 0.026 | 0.00049 |
| | 2596-83: Cat | | | 0.0039: 12 gram collar | | 0.018 | 0.00035 |
| | | | | 0.0080: 25 gram collar | | 0.038 | 0.00072 |
| | 2596-84: Dog | | | 0.0061: 19 gram collar | | 0.029 | 0.00055 |
| | | | | 0.010: 32 gram collar | | 0.049 | 0.00092 |
| | 2596-139: Cat | | | 0.0032: 10 gram collar | | 0.015 | 0.00029 |
| | 2596-139: Dog | | | 0.016: 50 gram collar | | 0.076 | 0.00144 |
| | 11556-164: Dog | | | 0.0072: 24 gram collar | | 0.034 | 0.00065 |
| | 11556-165: Cat | | | 0.0045: 15 gram collar | | 0.021 | 0.00041 |

| Table G.2. Residential Handler Non-cancer Risk Estimates Assuming 1/99 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 1/99 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 1/99 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 1/99 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0170 | 0.00032 | 4,100 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0285 | 0.00054 | 2,400 |
| | | 0.010: 32 gram collar | | 0.0481 | 0.00092 | 1,400 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0225 | 0.00043 | 3,100 |
| | | 0.0055: 17 gram collar | | 0.0255 | 0.00049 | 2,700 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0180 | 0.00034 | 3,800 |
| | | 0.0080: 25 gram collar | | 0.0376 | 0.00072 | 1,800 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0285 | 0.00054 | 2,400 |
| | | 0.010: 32 gram collar | | 0.0481 | 0.00092 | 1,400 |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0150 | 0.00029 | 4,600 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0751 | 0.00143 | 920 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0338 | 0.00064 | 2,000 |
| | 11556-165: Cat | 0.0045: 15 gram collar | | 0.0211 | 0.00040 | 3,300 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 1/99 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.01) + (Dust dermal dose * 0.99)

4 Combined 1/99 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.01) + (Dust dermal dose * 0.99)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 1/99 Liquid/Dust Inhalation Dose (mg/kg/day)

**Table G.3. Residential Handler Non-cancer Risk Estimates Assuming 50/50 Liquid/Dust Ratio Formulation Pet Collars.**

| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 50/50 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 50/50 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
|---|---|---|---|---|---|---|
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0092 | 0.00016 | 8,000 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0154 | 0.00028 | 4,800 |
| | | 0.010: 32 gram collar | | 0.0260 | 0.00046 | 2,800 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0122 | 0.00022 | 6,000 |
| | | 0.0055: 17 gram collar | | 0.0138 | 0.00025 | 5,300 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0097 | 0.00017 | 7,600 |
| | | 0.0080: 25 gram collar | | 0.0203 | 0.00036 | 3,600 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0154 | 0.00028 | 4,800 |
| | | 0.010: 32 gram collar | | 0.0260 | 0.00046 | 2,800 |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0081 | 0.00014 | 9,100 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0406 | 0.00072 | 1,800 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0183 | 0.00033 | 4,000 |
| | 11556-165: | 0.0045: | | 0.0114 | 0.00020 | 6,400 |

| Table G.3. Residential Handler Non-cancer Risk Estimates Assuming 50/50 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 50/50 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 50/50 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| | Cat | 15 gram collar | | | | |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 50/50 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.5) + (Dust dermal dose * 0.5)
4 Combined 50/50 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.5) + (Dust dermal dose * 0.5)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 50/50 Liquid/Dust Inhalation Dose (mg/kg/day)

| Table G.4. Residential Handler Non-cancer Risk Estimates Assuming 99/1 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 99/1 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 99/1 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| Application of TCVP Collars | 2596-49: Cat | 0.0036: 11 gram collar | 2 animals treated per day | 0.0014 | 3.27E-06 | 400,000 |
| | 2596-50, 62: Dog | 0.0061: 19 gram collar | | 0.0023 | 5.49E-06 | 240,000 |
| | | 0.010: 32 gram collar | | 0.0039 | 9.25E-06 | 140,000 |
| | 2596-63: Cat | 0.0048: 15 gram collar | | 0.0018 | 4.33E-06 | 300,000 |
| | | 0.0055: 17 gram collar | | 0.0021 | 4.91E-06 | 270,000 |
| | 2596-83: Cat | 0.0039: 12 gram collar | | 0.0015 | 3.47E-06 | 380,000 |
| | | 0.0080: 25 gram collar | | 0.0030 | 7.22E-06 | 180,000 |
| | 2596-84: Dog | 0.0061: 19 gram collar | | 0.0023 | 5.49E-06 | 240,000 |
| | | 0.010: | | 0.0039 | 9.25E-06 | 140,000 |

| Table G.4. Residential Handler Non-cancer Risk Estimates Assuming 99/1 Liquid/Dust Ratio Formulation Pet Collars. | | | | | | |
|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Combined 99/1 Liquid/Dust Dermal Dose (mg/kg/day)[3] | Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)[4] | Combined 99/1 Liquid/Dust Ratio Inhalation MOE[5] LOC = 300 |
| | | 32 gram collar | | | | |
| | 2596-139: Cat | 0.0032: 10 gram collar | | 0.0012 | 2.89E-06 | 450,000 |
| | 2596-139: Dog | 0.016: 50 gram collar | | 0.0061 | 1.44E-05 | 91,000 |
| | 11556-164: Dog | 0.0072: 24 gram collar | | 0.0027 | 6.51E-06 | 200,000 |
| | 11556-165: Cat | 0.0045: 15 gram collar | | 0.0017 | 4.07E-06 | 320,000 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Combined 99/1 Liquid/Dust Dermal Dose = (Liquid dermal dose * 0.99) + (Dust dermal dose * 0.01)
4 Combined 99/1 Liquid/Dust Inhalation Dose = (Liquid dermal dose * 0.99) + (Dust dermal dose * 0.01)
5. No dermal MOE estimated due to lack of dermal hazard. Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Combined 99/1 Liquid/Dust Inhalation Dose (mg/kg/day)

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| Application of TCVP Dusts/Powders | 47000-123: Dog | Inhalation: 300 | 1,700 | 3.1 | 0.00037: small | 2 animals treated per day | 0.0018 | N/A, No Dermal Hazard | 0.000034 | 39,000 |
| | | | | | 0.00094: medium | | 0.0044 | | 0.000084 | 16,000 |
| | | | | | 0.0015: large | | 0.0071 | | 0.00013 | 9,700 |
| | 47000-123: Cat | | | | 0.000094: small | | 0.00044 | | 0.0000084 | 160,000 |
| | | | | | 0.00023: medium | | 0.0011 | | 0.000020 | 65,000 |

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| | | | | | 0.00034: large | | 0.0016 | | 0.000030 | 43,000 |
| | 2596-78: Cat | | | | 0.00062: small | | 0.0029 | | 0.000056 | 24,000 |
| | | | | | 0.0010: large | | 0.0049 | | 0.000093 | 14,000 |
| | 2596-79; Dog | | | | 0.0010: small | | 0.0049 | | 0.000093 | 14,000 |
| | | | | | 0.0021: medium | | 0.0097 | | 0.00019 | 7,100 |
| | | | | | 0.0026: large | | 0.0122 | | 0.00023 | 5,600 |
| | 67517-82: Dog | | | | 0.0011: small | | 0.0053 | | 0.00010 | 13,000 |
| | | | | | 0.0028: medium | | 0.013 | | 0.00025 | 5,200 |
| | | | | | 0.0045: large | | 0.021 | | 0.00040 | 3,200 |
| | 67517-82: Cat | | | | 0.00028: small | | 0.0013 | | 0.000025 | 52,000 |
| | | | | | 0.00067: medium | | 0.0032 | | 0.000061 | 22,000 |
| | | | | | 0.0010: large | | 0.0048 | | 0.000091 | 14,000 |
| Application of TCVP Pump/Trigger Sprays | 2596-126, -140: Cat (Trigger) | | 820 | 3.3 | 0.00055: small | | 0.0013 | N/A, No Dermal Hazard | 0.000053 | 25000 |
| | | | | | 0.00077: medium | | 0.0018 | | 0.000074 | 18000 |
| | 2596-140 Cat (Pump) | | | | 0.00011: small | | 0.00026 | | 0.000011 | 120,000 |
| | | | | | 0.00016: large | | 0.00036 | | 0.000015 | 87,000 |

| Table G.5. Residential Handler Non-cancer Exposure and Risk Estimates from Use of TCVP Dust/Powder and Pump/Trigger Spray Products. Inhalation LOC is an MOE = 300; No dermal hazard. | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Reg. No. | Level of Concern | Dermal Unit Exposure (mg/lb ai) | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] (lb ai/pet) | Amount Handled Daily[2] | Dermal | | Inhalation | |
| | | | | | | | Dose (mg/kg/day)[3] | MOE[4] | Dose (mg/kg/day)[5] | MOE[6] |
| | 2596-125, -140: Dog (Trigger) | | | | 0.00077: small | | 0.0018 | | 0.000074 | 18,000 |
| | | | | | 0.00088: medium | | 0.0020 | | 0.000084 | 16,000 |
| | | | | | 0.0015: large | | 0.0035 | | 0.00015 | 8,900 |

1 Based on registered TCVP pet product labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide)
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/pet) × Area Treated or Amount Handled (pets/day) × Dermal Absorption Factor (9.6 %) ÷ Body Weight (69 kg). Dermal dose presented only for purpose of calculation of cancer risks for residential handlers.
4 No dermal MOE estimated due to lack of dermal hazard.
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/pet) × Area Treated or Amount Handled (pets/day) ÷ Body Weight (69 kg).
6 Inhalation MOE = Inhalation HED (1.31 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## Appendix H. Summary of Residential Handler Cancer Exposure and Risk Estimates

**Table H.1. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 1/99 Liquid/Dust Formulation Approach.**

| Reg No./ Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | 1/99 Liquid/Dust Cancer Risk Estimate[3] |
|---|---|---|---|---|---|
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 2.2E-07 |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.7E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 6.3E-07 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 3.0E-07 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 3.3E-07 |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 2.4E-07 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 4.9E-07 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.7E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 6.3E-07 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 2.0E-07 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 9.8E-07 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 4.4E-07 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 2.8E-07 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.01) + (Dust LADD * 0.99)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table H.2. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 50/50 Liquid/Dust Formulation Approach**

| Reg No./ Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | 50/50 Liquid/Dust Cancer Risk Estimate[3] |
|---|---|---|---|---|---|
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 1.2E-07 |

| Table H.2. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 50/50 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 2.0E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 3.4E-07 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 1.6E-07 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 1.8E-07 |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 1.3E-07 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 2.7E-07 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 2.0E-07 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 3.4E-07 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 1.1E-07 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 5.3E-07 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 2.4E-07 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 1.5E-07 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.5) + (Dust LADD * 0.5)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table H.3. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 99/1 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-49: Cat | Any | Adult | 8.5E-06 | 1.2E-04 | 1.8E-08 |
| 2596-50, 62: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.0E-08 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 5.0E-08 |
| 2596-63: Cat | Small | | 1.1E-05 | 1.6E-04 | 2.3E-08 |
| | Medium, Large | | 1.3E-05 | 1.8E-04 | 2.7E-08 |

| Table H.3. Residential Handler Cancer Exposure and Risk Estimates from TCVP Pet Collar Products Using 99/1 Liquid/Dust Formulation Approach | | | | | |
|---|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **50/50 Liquid/Dust Cancer Risk Estimate[3]** |
| 2596-83: Cat | Small | | 9.0E-06 | 1.3E-04 | 1.9E-08 |
| | Medium, Large | | 1.9E-05 | 2.7E-04 | 3.9E-08 |
| 2596-84: Dog | Small | | 1.4E-05 | 2.1E-04 | 3.0E-08 |
| | Medium, Large | | 2.4E-05 | 3.5E-04 | 5.0E-08 |
| 2596-139: Cat | Any | | 7.5E-06 | 1.1E-04 | 1.6E-08 |
| 2596-139: Dog | Any | | 3.8E-05 | 5.4E-04 | 7.8E-08 |
| 11556-164: Dog | Any | | 1.7E-05 | 2.4E-04 | 3.5E-08 |
| 11556-165: Cat | Any | | 1.1E-05 | 1.5E-04 | 2.2E-08 |

1 Liquid LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]. Inhalation exposures considered negligible based on use of spot-on data for liquid pet collar formulation.

2 Dust LADD = [Inhalation + Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

3 Cancer risk estimates = [(Liquid LADD * 0.99) + (Dust LADD * 0.01)] × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table H.4. Residential Handler Dermal and Inhalation Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Total LADD[1,2]** | **Cancer Risk Estimate[3]** |
| **Dust/Powder** | | | | |
| 47000-123: Dog | Small | Adult | 1.9E-05 | 3.5E-08 |
| | Medium | | 4.7E-05 | 8.7E-08 |
| | Large | | 7.6E-05 | 1.4E-07 |
| 47000-123: Cat | Small | | 4.7E-06 | 8.7E-09 |
| | Medium | | 1.1E-05 | 2.1E-08 |
| | Large | | 1.7E-05 | 3.1E-08 |
| 2596-78: Cat | Small | | 3.1E-05 | 5.7E-08 |
| | Medium | | 5.2E-05 | 9.6E-08 |

| Table H.4. Residential Handler Dermal and Inhalation Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Reg No./ Animal Type** | **Animal Size** | **Lifestage** | **Total LADD[1,2]** | **Cancer Risk Estimate[3]** |
| 2596-79: Dog | Small | Adult | 5.2E-05 | 9.6E-08 |
| | Medium | | 1.0E-04 | 1.9E-07 |
| | Large | | 1.3E-04 | 2.4E-07 |
| 67517-82: Dog | Small | | 5.7E-05 | 1.0E-07 |
| | Medium | | 1.4E-04 | 2.6E-07 |
| | Large | | 2.3E-04 | 4.2E-07 |
| 67517-82: Cat | Small | | 1.4E-05 | 2.6E-08 |
| | Medium | | 3.4E-05 | 6.2E-08 |
| | Large | | 5.1E-05 | 9.4E-08 |
| **Pump/Trigger Sprays** | | | | |
| 2596-126: -140: Cat (Trigger) | Small | | 1.4E-05 | 2.5E-08 |
| | Large | | 1.9E-05 | 3.5E-08 |
| 2596-140: Cat (Pump) | Small | | 2.8E-06 | 5.1E-09 |
| | Large | | 3.9E-06 | 7.2E-09 |
| 2596-125, -140: Dog (Trigger) | Small | | 1.9E-05 | 3.5E-08 |
| | Medium | | 2.2E-05 | 4.0E-08 |
| | Large | | 3.9E-05 | 7.0E-08 |

1 Total Lifetime Average Daily Dose (LADD, mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
2 Dermal and Inhalation LADD equations provided in Appendix B.
3 Cancer risk estimates = Total LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

## Appendix I. Summary of Residential Post-Application Non-Cancer Exposure and Risk Estimates

**Table I.1. Residential Post-application Non-cancer Incidental Oral Dose Assuming a Liquid or Dust Formulation for Pet Collars.**

| Animal Type | Animal Size | Application Rate (mg ai) | $F_{ai hands}$ | DE<br>Dermal Exposure (mg) | $SA_H$<br>Surface area of 1 hand ($cm^2$) | HR<br>Hand residue loading ($mg/cm^2$) | $F_m$<br>Fraction of hand mouthed | ET<br>Exposure Time (hours/day) | Replenish-ment interval (min) | N_Replen<br># replenish-ment intervals per hour (intervals/hr) | SE<br>Fraction Saliva Extraction | Freq_HtM<br>Number of hand-to-mouth contacts events per hour (events/hr) | Incidental oral Absorbed Dose (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assume Liquid Formulation -- Use of Davis Study (2008) and Liquid TCs** | | | | | | | | | | | | | |
| Cat (2596-49) | small | 1650 | 0.04 | 6.1 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0056 |
| | medium | 1650 | 0.04 | 3.7 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0033 |
| | large | 1650 | 0.04 | 2.3 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Dog (2596-50,62) | small | 2774 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0047 |
| | large | 4672 | 0.04 | 2.4 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Cat (2596-83) | small | 1752 | 0.04 | 6.5 | 150 | 0.0009 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0059 |
| | large | 3650 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0046 |
| Cat (2596-139) | small | 1460 | 0.04 | 5.4 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0049 |
| | medium | 1460 | 0.04 | 3.2 | 150 | 0.0004 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0030 |
| | large | 1460 | 0.04 | 2.0 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0018 |
| Dog (11556-164) | small | 3288 | 0.04 | 6.1 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0055 |
| | medium | 3288 | 0.04 | 2.6 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0024 |
| | large | 3288 | 0.04 | 1.7 | 150 | 0.0002 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0015 |
| Cat (11556-165) | small | 2055 | 0.04 | 7.6 | 150 | 0.0010 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0069 |
| | medium | 2055 | 0.04 | 4.6 | 150 | 0.0006 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0042 |
| | large | 2055 | 0.04 | 2.9 | 150 | 0.0004 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0026 |
| Dog (2596-84) | small | 2774 | 0.04 | 5.1 | 150 | 0.0007 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0047 |
| | large | 4672 | 0.04 | 2.4 | 150 | 0.0003 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0021 |
| Dog (2596-139) | small | 7300 | 0.04 | 13.5 | 150 | 0.0018 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0123 |
| | medium | 7300 | 0.04 | 5.8 | 150 | 0.0008 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0053 |
| | large | 7300 | 0.04 | 3.7 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0034 |
| Cat (2596-63) | small | 2190 | 0.04 | 8.1 | 150 | 0.0011 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0074 |
| | large | 2482 | 0.04 | 3.5 | 150 | 0.0005 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.0031 |
| **Assume Dust Formulation -- Use of Davis Study (2008) and Dust TCs** | | | | | | | | | | | | | |
| Cat (2596-49) | small | 1650 | 0.37 | 166 | 150 | 0.2049 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.40 |
| | medium | 1650 | 0.37 | 100 | 150 | 0.1229 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.84 |
| | large | 1650 | 0.37 | 62 | 150 | 0.0768 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.52 |
| Dog (2596-50,62) | small | 2774 | 0.37 | 140 | 150 | 0.1723 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.18 |
| | large | 4672 | 0.37 | 64 | 150 | 0.0791 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.54 |
| Cat (2596-83) | small | 1752 | 0.37 | 176 | 150 | 0.2176 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.48 |

**Table I.1. Residential Post-application Non-cancer Incidental Oral Dose Assuming a Liquid or Dust Formulation for Pet Collars.**

| Animal Type | Animal Size | Application Rate (mg ai) | $F_{aihands}$ | DE Dermal Exposure (mg) | $SA_H$ Surface area of 1 hand ($cm^2$) | HR Hand residue loading ($mg/cm^2$) | $F_m$ Fraction of hand mouthed | ET Exposure Time (hours/day) | Replenish-ment interval (min) | N_Replen # replenish-ment intervals per hour (intervals/hr) | SE Fraction Saliva Extraction | Freq_HtM Number of hand-to-mouth contacts events per hour (events/hr) | Incidental oral Absorbed Dose (mg/kg/day) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | large | 3650 | 0.37 | 138 | 150 | 0.1700 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.16 |
| Cat (2596-139) | small | 1460 | 0.37 | 147 | 150 | 0.1813 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.24 |
| | medium | 1460 | 0.37 | 88 | 150 | 0.1088 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.74 |
| | large | 1460 | 0.37 | 55 | 150 | 0.0680 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.46 |
| Dog (11556-164) | small | 3288 | 0.37 | 166 | 150 | 0.2042 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.39 |
| | medium | 3288 | 0.37 | 71 | 150 | 0.0875 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.60 |
| | large | 3288 | 0.37 | 45 | 150 | 0.0557 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.38 |
| Cat (11556-165) | small | 2055 | 0.37 | 207 | 150 | 0.2552 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.74 |
| | medium | 2055 | 0.37 | 124 | 150 | 0.1531 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.04 |
| | large | 2055 | 0.37 | 78 | 150 | 0.0957 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.65 |
| Dog (2596-84) | small | 2774 | 0.37 | 140 | 150 | 0.1723 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.18 |
| | large | 4672 | 0.37 | 64 | 150 | 0.0791 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.54 |
| Dog (2596-139) | small | 7300 | 0.37 | 368 | 150 | 0.4533 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 3.09 |
| | medium | 7300 | 0.37 | 158 | 150 | 0.1943 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.33 |
| | large | 7300 | 0.37 | 100 | 150 | 0.1236 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.84 |
| Cat (2596-63) | small | 2190 | 0.37 | 221 | 150 | 0.2720 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 1.86 |
| | large | 2482 | 0.37 | 94 | 150 | 0.1156 | 0.13 | 1 | 15 | 4 | 0.48 | 20 | 0.79 |

1. Application rates are label defined. Refer to D426984.
2. Dermal Exposure (mg/day) = [Transfer Coefficient ($cm^2$/hr)] * [Application Rate (label defined) * Fraction Application Rate (0.0040; Davis, M. Et. al) ÷ Surface Area of Cat/Dog (Cat: Small, 1,500; Medium, 2,500; Large, 4,000 $cm^2$ - Dog: Small, 3,000; Medium, 7,000; Large, 11,000 $cm^2$)] x [Exposure Time (Adults, 0.77 hours/day; Children, 1.0 hours/day))
3. Incidental Oral Dose (mg/kg/day) = [Hand Residue Loading ($mg/cm^2$)] × [Fraction of Hand Mouthed (0.13) × Surface Area of 1 Child Hand (150 $cm^2$ )] x [Exposure Time (1.0 hrs/day) × # of Replenishment Intervals/hr (4 int/hr)) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (20 events/hr) ) ÷ ( # of Replenishment Intervals/hr))] / [Body Weight (11 kg child 1 to < 2 years old years old)]
   Where the Hand Residue Loading ($mg/cm^2$) = [$Fai_{hands}$ (Solid, 0.37; Liquids; 0.040) x Dermal Exposure (mg/day)] ÷ [Surface Area of 1 Child Hand (150 $cm^2$) x 2]

| Table I.2. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 1/99 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 1/99 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **2** |
| | | | Medium | 0.00334 | 0.83861 | **3.4** |
| | | | Large | 0.00209 | 0.52413 | **5.4** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **2.4** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **5.2** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **1.9** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **2.4** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **2.3** |
| | | | Medium | 0.00296 | 0.74213 | **3.8** |
| | | | Large | 0.00185 | 0.46383 | **6.1** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **2** |
| | | | Medium | 0.00238 | 0.59690 | **4.7** |
| | | | Large | 0.00151 | 0.37985 | **7.4** |
| 11556-165: Cat | Children 1 < 2 | 2,060 | Small | 0.00693 | 1.74096 | **1.6** |
| | | | Medium | 0.00416 | 1.04458 | **2.7** |
| | | | Large | 0.00260 | 0.65286 | **4.3** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **2.4** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **5.2** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **0.91** |
| | | | Medium | 0.00528 | 1.32524 | **2.1** |
| | | | Large | 0.00336 | 0.84333 | **3.4** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **1.5** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **3.6** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.01) + (Dust HtM Dose * 0.99)]. Bolded MOEs indicate a risk of concern.

| Table I.3. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 50/50 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 50/50 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **4** |
| | | | Medium | 0.00334 | 0.83861 | **6.7** |
| | | | Large | 0.00209 | 0.52413 | **11** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **4.7** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **10** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **3.8** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **4.8** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **4.5** |
| | | | Medium | 0.00296 | 0.74213 | **7.5** |
| | | | Large | 0.00185 | 0.46383 | **12** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **4** |
| | | | Medium | 0.00238 | 0.59690 | **9.3** |
| | | | Large | 0.00151 | 0.37985 | **15** |
| 11556-165: Cat | Children | 2,060 | Small | 0.00693 | 1.74096 | **3.2** |

| Table I.3. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 50/50 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 50/50 Liquid/Dust Combined MOE[4] |
| | 1 < 2 | | Medium | 0.00416 | 1.04458 | **5.3** |
| | | | Large | 0.00260 | 0.65286 | **8.5** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **4.7** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **10** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **1.8** |
| | | | Medium | 0.00528 | 1.32524 | **4.2** |
| | | | Large | 0.00336 | 0.84333 | **6.6** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **3** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **7.1** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.5) + (Dust HtM Dose * 0.5)]. Bolded MOEs indicate a risk of concern.

| Table I.4. Residential Post-Application Non-Cancer Incidental Oral Exposure Estimates from TCVP Pet Collars. 99/1 Ratio Liquid to Dust/Solid Formulation. Incidental Oral LOC is an MOE = 1,000. | | | | | | |
|---|---|---|---|---|---|---|
| EPA Reg. No./ Animal | Lifestage | Application Rate (mg ai)[1] | Animal Size | Liquid HtM Dose (mg/kg/day)[2] | Dust HtM Dose (mg/kg/day)[3] | 99/1 Liquid/Dust Combined MOE[4] |
| 2596-49: Cat | Children 1 < 2 | 1,650 | Small | 0.00557 | 1.39768 | **140** |
| | | | Medium | 0.00334 | 0.83861 | **240** |
| | | | Large | 0.00209 | 0.52413 | **380** |
| 2596-50, 62: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **170** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **370** |
| 2596-83: Cat | Children 1 < 2 | 1,750 | Small | 0.00591 | 1.48427 | **140** |
| | | 3,650 | Large | 0.00462 | 1.15958 | **170** |
| 2596-139: Cat | Children 1 < 2 | 3,650 | Small | 0.00493 | 1.23689 | **160** |
| | | | Medium | 0.00296 | 0.74213 | **270** |
| | | | Large | 0.00185 | 0.46383 | **430** |
| 11556-164: Dog | Children 1 < 2 | 3,290 | Small | 0.00555 | 1.39277 | **140** |
| | | | Medium | 0.00238 | 0.59690 | **340** |
| | | | Large | 0.00151 | 0.37985 | **530** |
| 11556-165: Cat | Children 1 < 2 | 2,060 | Small | 0.00693 | 1.74096 | **120** |
| | | | Medium | 0.00416 | 1.04458 | **190** |
| | | | Large | 0.00260 | 0.65286 | **310** |
| 2596-84: Dog | Children 1 < 2 | 2,770 | Small | 0.00468 | 1.17504 | **170** |
| | | 4,670 | Large | 0.00215 | 0.53973 | **370** |
| 2596-139: Dog | Children 1 < 2 | 7,300 | Small | 0.01232 | 3.09222 | **65** |
| | | | Medium | 0.00528 | 1.32524 | **150** |
| | | | Large | 0.00336 | 0.84333 | **240** |
| 2596-63: Cat | Children 1 < 2 | 2,190 | Small | 0.00739 | 1.85533 | **110** |
| | | 2,480 | Large | 0.00314 | 0.78852 | **250** |

1. Application rates are label defined. Refer to D426984.
2. Liquid and Dust HTM Doses from Table E.1
3. 1/99 Liquid/Dust Combined MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ [(Liquid HtM Dose * 0.99) + (Dust HtM Dose * 0.01)]. Bolded MOEs indicate a risk of concern.

| Table I.5. Residential Post-Application Non-Cancer Exposure and Risk Estimates from TCVP Dust/Powder and Pump/Trigger Spray Formulations. Incidental Oral LOC is an MOE = 1,000 | | | | | | |
|---|---|---|---|---|---|---|
| **EPA Reg. No./ Animal** | **Lifestage** | **Application Rate (mg ai)[1]** | **Animal Size** | **Dermal Exposure (mg/day)[2]** | **Incidental Oral Dose (mg/kg/day)[3]** | **MOE[4]** |
| **Dusts/Powders** | | | | | | |
| 47000-123: Dog | Children 1 < 2 | 170 | Small | 1.0 | 0.0087 | **320** |
| | | 430 | Medium | 1.1 | 0.0093 | **300** |
| | | 680 | Large | 1.1 | 0.0095 | **300** |
| 47000-123: Cat | Children 1 < 2 | 43 | Small | 0.52 | 0.0043 | **640** |
| | | 100 | Medium | 0.74 | 0.0063 | **450** |
| | | 150 | Large | 0.70 | 0.0059 | **480** |
| 2596-78: Cat | Children 1 < 2 | 280 | Small | 3.4 | 0.0287 | **98** |
| | | 470 | Large | 2.1 | 0.0180 | **160** |
| 2596-79: Dog | Children 1 < 2 | 470 | Small | 2.9 | 0.0240 | **120** |
| | | 940 | Medium | 2.4 | 0.0205 | **140** |
| | | 1,200 | Large | 1.9 | 0.0163 | **170** |
| 67517-82: Dog | Children 1 < 2 | 510 | Small | 3.1 | 0.0261 | **110** |
| | | 1,300 | Medium | 3.3 | 0.0280 | **100** |
| | | 2,000 | Large | 3.4 | 0.0285 | **98** |
| 67517-82: Cat | Children 1 < 2 | 130 | Small | 1.6 | 0.0130 | **210** |
| | | 310 | Medium | 2.2 | 0.0188 | **150** |
| | | 460 | Large | 2.1 | 0.0176 | **160** |
| **Pump/Trigger Sprays** | | | | | | |
| 2596-126, 140: Cat (Trigger) | Children 1 < 2 | 250 | Small | 1.9 | 0.00172 | 1,600 |
| | | 350 | Large | 0.99 | 0.00090 | 3,100 |
| 2596-140: Cat (Pump) | Children 1 < 2 | 51 | Small | 0.39 | 0.00035 | 8,000 |
| | | 71 | Large | 0.20 | 0.00018 | 15,000 |
| 2596-125, -140: Dog (Trigger) | Children 1 < 2 | 350 | Small | 1.3 | 0.00120 | 2,300 |
| | | 400 | Medium | 0.65 | 0.00059 | 4,800 |
| | | 700 | Large | 0.72 | 0.00066 | 4,300 |

1. Application rates are label defined. Refer to D426984.
2. Dermal Exposure (mg/day) = [Transfer Coefficient ($cm^2$/hr)] * [Application Rate (label defined) * Fraction Application Rate (Dust, 0.00048; Spray, 0.0081) ÷ Surface Area of Cat/Dog (Cat: Small, 1,500; Medium, 2,500; Large, 4,000 $cm^2$ - Dog: Small, 3,000; Medium, 7,000; Large, 11,000 $cm^2$)] x [Exposure Time (Adults, 0.77 hours/day; Children, 1.0 hours/day))]
3. Incidental Oral Dose (mg/kg/day) = [Hand Residue Loading (mg/$cm^2$)] × [Fraction of Hand Mouthed (0.13) × Surface Area of 1 Child Hand (150 $cm^2$ )] x [Exposure Time (1.0 hrs/day) × # of Replenishment Intervals/hr (4 int/hr)) × (1-((1-Saliva Extraction Factor (0.5))^(Number of Hand-to-Mouth Events per Hour (20 events/hr) ) ÷ ( # of Replenishment Intervals/hr))] / [Body Weight (11 kg child 1 to < 2 years old years old)]
   Where the Hand Residue Loading (mg/$cm^2$) = [$Fai_{hands}$ (Dusts, 0.37; Liquids; 0.040) x Dermal Exposure (mg/day)] ÷ [Surface Area of 1 Child Hand (150 $cm^2$) x 2]
4. MOE = Incidental Oral NOAEL (2.8 mg/kg/day) ÷ Incidental Oral Dose (mg/kg/day). Bolded MOEs indicate a risk of concern.

## Appendix J. Summary of Residential Post-Application Cancer Exposure and Risks

| Table J.1. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar – 1/99 Ratio of Liquid/Dust Formulation | | | | | | |
|---|---|---|---|---|---|---|
| **Animal Type** | **Animal Size** | **Lifestage** | **Liquid LADD[1]** | **Dust LADD[2]** | **Combined 1/99 Liquid/Dust LADD[3]** | **Cancer Risk Estimate[4]** |
| **Exposure Data Source: Davis, M., et al (2008)** | | | | | | |
| 2596-49: Cat | Small | Adult | 5.8E-03 | 1.6E-01 | 1.5E-01 | 2.8E-04 |
| | Medium | | 3.5E-03 | 9.4E-02 | 9.3E-02 | 1.7E-04 |
| | Large | | 2.2E-03 | 5.8E-02 | 5.8E-02 | 1.1E-04 |
| 2596-50,62: Dog | Small | | 4.9E-03 | 1.3E-01 | 1.3E-01 | 2.4E-04 |
| | Large | | 2.2E-03 | 6.0E-02 | 6.0E-02 | 1.1E-04 |
| 2596-83: Cat | Small | | 6.2E-03 | 1.7E-01 | 1.6E-01 | 3.0E-04 |
| | Large | | 4.8E-03 | 1.3E-01 | 1.3E-01 | 2.3E-04 |
| 2596-139: Cat | Small | | 5.1E-03 | 1.4E-01 | 1.4E-01 | 2.5E-04 |
| | Medium | | 3.1E-03 | 8.3E-02 | 8.2E-02 | 1.5E-04 |
| | Large | | 1.9E-03 | 5.2E-02 | 5.1E-02 | 9.4E-05 |
| 11556-164: Dog | Small | | 5.8E-03 | 1.6E-01 | 1.5E-01 | 2.8E-04 |
| | Medium | | 2.5E-03 | 6.7E-02 | 6.6E-02 | 1.2E-04 |
| | Large | | 1.6E-03 | 4.2E-02 | 4.2E-02 | 7.7E-05 |
| 11556-165: Cat | Small | | 7.2E-03 | 1.9E-01 | 1.9E-01 | 3.5E-04 |
| | Medium | | 4.3E-03 | 1.2E-01 | 1.2E-01 | 2.1E-04 |
| | Large | | 2.7E-03 | 7.3E-02 | 7.2E-02 | 1.3E-04 |
| 2596-84: Dog | Small | | 4.9E-03 | 1.3E-01 | 1.3E-01 | 2.4E-04 |
| | Large | | 2.2E-03 | 6.0E-02 | 6.0E-02 | 1.1E-04 |
| 2596-139: Dog | Small | | 1.3E-02 | 3.5E-01 | 3.4E-01 | 6.3E-04 |
| | Medium | | 5.5E-03 | 1.5E-01 | 1.5E-01 | 2.7E-04 |
| | Large | | 3.5E-03 | 9.4E-02 | 9.3E-02 | 1.7E-04 |
| 2596-63: Cat | Small | | 7.7E-03 | 2.1E-01 | 2.1E-01 | 3.8E-04 |
| | Large | | 3.3E-03 | 8.8E-02 | 8.7E-02 | 1.6E-04 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 1/99 Liquid/Dust LADD = (Liquid LADD * 0.01) + (Dust LADD * 0.99)

4 Cancer risk estimates = Combined 1/99 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table J.2. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar - 50/50 Ratio of Liquid and Solid Formulation**

| Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | Combined 50/50 Liquid/Dust LADD[3] | Cancer Risk Estimate[4] |
|---|---|---|---|---|---|---|
| 2596-49: Cat | Small | Adult | 2.9E-03 | 7.8E-02 | 8.1E-02 | 1.5E-04 |
| | Medium | | 1.7E-03 | 4.7E-02 | 4.9E-02 | 8.9E-05 |
| | Large | | 1.1E-03 | 2.9E-02 | 3.0E-02 | 5.5E-05 |
| 2596-50,62: Dog | Small | | 2.4E-03 | 6.6E-02 | 6.8E-02 | 1.2E-04 |
| | Large | | 1.1E-03 | 3.0E-02 | 3.1E-02 | 5.7E-05 |
| 2596-83: Cat | Small | | 3.1E-03 | 8.3E-02 | 8.6E-02 | 1.6E-04 |
| | Large | | 2.4E-03 | 6.5E-02 | 6.7E-02 | 1.2E-04 |
| 2596-139: Cat | Small | | 2.6E-03 | 6.9E-02 | 7.2E-02 | 1.3E-04 |
| | Medium | | 1.5E-03 | 4.1E-02 | 4.3E-02 | 7.9E-05 |
| | Large | | 9.6E-04 | 2.6E-02 | 2.7E-02 | 4.9E-05 |
| 11556-164: Dog | Small | | 2.9E-03 | 7.8E-02 | 8.1E-02 | 1.5E-04 |
| | Medium | | 1.2E-03 | 3.3E-02 | 3.5E-02 | 6.3E-05 |
| | Large | | 7.9E-04 | 2.1E-02 | 2.2E-02 | 4.0E-05 |
| 11556-165: Cat | Small | | 3.6E-03 | 9.7E-02 | 1.0E-01 | 1.8E-04 |
| | Medium | | 2.2E-03 | 5.8E-02 | 6.0E-02 | 1.1E-04 |
| | Large | | 1.4E-03 | 3.6E-02 | 3.8E-02 | 6.9E-05 |
| 2596-84: Dog | Small | | 2.4E-03 | 6.6E-02 | 6.8E-02 | 1.2E-04 |
| | Large | | 1.1E-03 | 3.0E-02 | 3.1E-02 | 5.7E-05 |
| 2596-139: Dog | Small | | 6.4E-03 | 1.7E-01 | 1.8E-01 | 3.3E-04 |
| | Medium | | 2.7E-03 | 7.4E-02 | 7.7E-02 | 1.4E-04 |
| | Large | | 1.7E-03 | 4.7E-02 | 4.9E-02 | 8.9E-05 |
| 2596-63: Cat | Small | | 3.8E-03 | 1.0E-01 | 1.1E-01 | 2.0E-04 |
| | Large | | 1.6E-03 | 4.4E-02 | 4.6E-02 | 8.3E-05 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 50/50 Liquid/Dust LADD = (Liquid LADD * 0.5) + (Dust LADD * 0.5)

4 Cancer risk estimates = Combined 50/50 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

**Table J.3. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Collar - 99/1 Ratio of Liquid and Solid Formulation**

| Animal Type | Animal Size | Lifestage | Liquid LADD[1] | Dust LADD[2] | Combined 99/1 Liquid/Dust LADD[3] | Cancer Risk Estimate[4] |
|---|---|---|---|---|---|---|
| 2596-49: Cat | Small | Adult | 5.7E-03 | 1.6E-03 | 7.3E-03 | 1.3E-05 |
| | Medium | | 3.4E-03 | 9.4E-04 | 4.4E-03 | 8.0E-06 |
| | Large | | 2.2E-03 | 5.8E-04 | 2.7E-03 | 5.0E-06 |
| 2596-50,62: Dog | Small | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| | Large | | 2.2E-03 | 6.0E-04 | 2.8E-03 | 5.2E-06 |
| 2596-83: Cat | Small | | 6.1E-03 | 1.7E-03 | 7.7E-03 | 1.4E-05 |
| | Large | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| 2596-139: Cat | Small | | 5.1E-03 | 1.4E-03 | 6.5E-03 | 1.2E-05 |
| | Medium | | 3.0E-03 | 8.3E-04 | 3.9E-03 | 7.1E-06 |
| | Large | | 1.9E-03 | 5.2E-04 | 2.4E-03 | 4.4E-06 |
| 11556-164: Dog | Small | | 5.7E-03 | 1.6E-03 | 7.3E-03 | 1.3E-05 |
| | Medium | | 2.4E-03 | 6.7E-04 | 3.1E-03 | 5.7E-06 |
| | Large | | 1.6E-03 | 4.2E-04 | 2.0E-03 | 3.6E-06 |
| 11556-165: Cat | Small | | 7.1E-03 | 1.9E-03 | 9.1E-03 | 1.7E-05 |
| | Medium | | 4.3E-03 | 1.2E-03 | 5.5E-03 | 1.0E-05 |
| | Large | | 2.7E-03 | 7.3E-04 | 3.4E-03 | 6.2E-06 |
| 2596-84: Dog | Small | | 4.8E-03 | 1.3E-03 | 6.1E-03 | 1.1E-05 |
| | Large | | 2.2E-03 | 6.0E-04 | 2.8E-03 | 5.2E-06 |
| 2596-139: Dog | Small | | 1.3E-02 | 3.5E-03 | 1.6E-02 | 3.0E-05 |
| | Medium | | 5.4E-03 | 1.5E-03 | 6.9E-03 | 1.3E-05 |
| | Large | | 3.5E-03 | 9.4E-04 | 4.4E-03 | 8.1E-06 |
| 2596-63: Cat | Small | | 7.6E-03 | 2.1E-03 | 9.7E-03 | 1.8E-05 |
| | Large | | 3.2E-03 | 8.8E-04 | 4.1E-03 | 7.5E-06 |

1 Liquid LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)].

2 Dust LADD = [Dermal Dose (mg/kg/day)] × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (yrs) ÷ Lifetime expectancy (yrs)]

3 Combined 99/1 Liquid/Dust LADD = (Liquid LADD * 0.99) + (Dust LADD * 0.01)

4 Cancer risk estimates = Combined 99/1 Liquid/Dust LADD × $Q_1^*$, where $Q_1^* = 1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

| Table J.4. Residential Post-Application Cancer Exposure and Risk Estimates from TCVP Pet Products | | | | |
|---|---|---|---|---|
| **Animal Type** | **Animal Size** | **Lifestage** | **LADD[1,2]** | **Cancer Risk Estimate[3]** |
| **Dust/Powder** | | | | |
| 47000-123: Dog | Small | Adult | 5.9E-04 | 1.1E-06 |
| | Medium | | 6.3E-04 | 1.2E-06 |
| | Large | | 6.4E-04 | 1.2E-06 |
| 47000-123: Cat | Small | | 2.9E-04 | 5.4E-07 |
| | Medium | | 4.2E-04 | 7.8E-07 |
| | Large | | 4.0E-04 | 7.3E-07 |
| 2596-78: Cat | Small | | 1.9E-03 | 3.6E-06 |
| | Large | | 1.2E-03 | 2.2E-06 |
| 2596-79: Dog | Small | | 1.6E-03 | 3.0E-06 |
| | Medium | | 1.4E-03 | 2.5E-06 |
| | Large | | 1.1E-03 | 2.0E-06 |
| 67517-82: Dog | Small | | 1.8E-03 | 3.2E-06 |
| | Medium | | 1.9E-03 | 3.5E-06 |
| | Large | | 1.9E-03 | 3.5E-06 |
| 67517-82: Cat | Small | | 8.8E-04 | 1.6E-06 |
| | Medium | | 1.3E-03 | 2.3E-06 |
| | Large | | 1.2E-03 | 2.2E-06 |
| **Pump/Trigger Spray** | | | | |
| 2596-126, 140: Cat (Trigger) | Small | Adult | 5.3E-04 | 9.6E-07 |
| | Large | | 2.8E-04 | 5.1E-07 |
| 2596-140: Cat (Pump) | Small | | 1.1E-04 | 2.0E-07 |
| | Large | | 5.6E-05 | 1.0E-07 |
| 2596-125, -140: Dog (Trigger) | Small | | 3.7E-04 | 6.7E-07 |
| | Medium | | 1.8E-04 | 3.3E-07 |
| | Large | | 2.0E-04 | 3.7E-07 |

1 Total Lifetime Average Daily Dose (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
2 Dermal and Inhalation LADD equations provided in Appendix B.
3 Cancer risk estimates = Total LADD × Q1*, where Q1* = $1.83 \times 10^{-3}$ $(mg/kg/day)^{-1}$

## Appendix K. Summary of Occupational Handler Non-Cancer Exposures and Risks



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| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Floors) | 0.00077 lb ai/sq ft | 100,000 (sq ft/day) | 2.5E-04 | 4.9E-05 | 2.5E-05 | 9.3E-05 | 16,000 | 81,000 | 160,000 | 43,000 |
| | Poultry Buildings (Floor Management, Fowl Tick) | 0.00064 lb ai/sq ft | | 2.0E-04 | 4.1E-05 | 2.0E-05 | 7.7E-05 | 19,000 | 97,000 | 190,000 | 51,000 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 4.1E-05 | 8.3E-06 | 4.1E-06 | 1.6E-05 | 95,000 | 480,000 | 950,000 | 250,000 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 2.0E-05 | 4.1E-06 | 2.0E-06 | 7.7E-06 | 190,000 | 970,000 | 1,900,000 | 510,000 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 4.9E-07 | 9.8E-08 | 4.9E-08 | 1.9E-07 | 8.1E+06 | 4.0E+07 | 8.1E+07 | 2.1E+07 |
| | | 0.064 lb ai/gallon | | 4.1E-07 | 8.1E-08 | 4.1E-08 | 1.5E-07 | 9.7E+06 | 4.8E+07 | 9.7E+07 | 2.6E+07 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick) | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.050 | 0.010 | 0.0050 | 0.00028 | **79** | 400 | 790 | 14,000 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 0.020 | 0.040 | 0.0020 | 0.00011 | **200** | 990 | 2,000 | 35,000 |
| (2b) Mixing/ Loading Wettable Powders for Paint Applications | Poultry (Floor Management – Roost) | 0.080 lb ai/gallon | 2 gallons | 1.0E-04 | 2.0E-05 | 1.0E-05 | 5.6E-07 | 40,000 | 200,000 | 400,000 | 7,100,000 |
| (3a) Mixing/ Loading Dusts for | | 0.030 lb ai/gallon | | 3.7E-05 | 7.5E-06 | 3.7E-06 | 2.1E-07 | 110,000 | 530,000 | 1,100,000 | 1.9E+07 |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Paint Applications (WP Data as Surrogate) | | | | | | | | | | | |
| **Applicators** | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 3.9E-04 | 7.9E-05 | 3.9E-05 | 5.0E-05 | 10,000 | 50,000 | 100,000 | 79,000 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 3.8E-04 | 7.6E-05 | 3.8E-05 | 4.8E-05 | 10,000 | 52,000 | 100,000 | 82,000 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3.2E-04 | 6.3E-05 | 3.2E-05 | 4.0E-05 | 12,000 | 63,000 | 120,000 | 99,000 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 1.6E-04 | 3.2E-05 | 1.6E-05 | 2.0E-05 | 25,000 | 120,000 | 250,000 | 200,000 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 6.4E-05 | 1.3E-05 | 6.4E-06 | 8.1E-06 | 61,000 | 310,000 | 610,000 | 490,000 |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 3.2E-05 | 6.3E-06 | 3.2E-06 | 4.0E-06 | 120,000 | 630,000 | 1,200,000 | 990,000 |
| (5) Open Pour Liquid Additive for | Cattle Feed (Concentrate) | 0.0039 lb ai/animal | 1,000 cows | 1.2E-05 | 2.5E-06 | 1.2E-06 | No Data | 320,000 | 1,600,000 | 3,200,000 | No Data |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 7.0E-06 | 1.4E-06 | 7.0E-07 | No Data | 560,000 | 2,800,000 | 5,600,000 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Feed Through Applications | Horse Feed | 0.0017 lb ai/animal | 500 horses | 2.7E-06 | 5.4E-07 | 2.7E-07 | No Data | 1,500,000 | 7,300,000 | 15,000,000 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 1.2E-05 | 2.4E-06 | 1.2E-06 | No Data | 330,000 | 1,700,000 | 3,300,000 | No Data |
| (6a) RTU Pet Collars - 1/99 liquid/dust ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 0.0072 | 0.0014 | 0.00072 | No Data | 550 | 2,700 | 5,500 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.012 | 0.0025 | 0.0012 | No Data | 320 | 1,600 | 3,200 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.020 | 0.0040 | 0.0020 | No Data | **200** | 980 | 2,000 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.0096 | 0.0019 | 0.00096 | No Data | 410 | 2,100 | 4,100 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.011 | 0.0022 | 0.0011 | No Data | 360 | 1,800 | 3,600 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.0078 | 0.0016 | 0.00078 | No Data | 500 | 2,500 | 5,000 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.016 | 0.0032 | 0.0016 | No Data | **250** | 1,200 | 2,500 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.012 | 0.0025 | 0.0012 | No Data | 320 | 1,600 | 3,200 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.020 | 0.0040 | 0.0020 | No Data | **200** | 980 | 2,000 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.0064 | 0.0013 | 0.00064 | No Data | 610 | 3,100 | 6,100 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.032 | 0.0064 | 0.0032 | No Data | **120** | 610 | 1,200 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.014 | 0.0029 | 0.0014 | No Data | **270** | 1,400 | 2,700 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.0090 | 0.0018 | 0.00090 | No Data | 440 | 2,200 | 4,400 | No Data |
| (6b) RTU Pet Collars - 50/50 | Cat (2596-49) | 0.0036 lb ai/animal | | 0.0037 | 0.00073 | 0.00037 | No Data | 1,100 | 5,400 | 11,000 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.0062 | 0.0012 | 0.00062 | No Data | 640 | 3,200 | 6,400 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| liquid/dust ratio | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.010 | 0.0020 | 0.0010 | No Data | 390 | 1,900 | 3,900 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.0049 | 0.00097 | 0.00049 | No Data | 810 | 4,100 | 8,100 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 700 | 3,500 | 7,000 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.0040 | 0.00079 | 0.00040 | No Data | 1,000 | 5,000 | 10,000 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.0081 | 0.0016 | 0.00081 | No Data | 490 | 2,400 | 4,900 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.0062 | 0.0012 | 0.00062 | No Data | 640 | 3,200 | 6,400 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.010 | 0.0020 | 0.0010 | No Data | 390 | 1,900 | 3,900 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.0032 | 0.00065 | 0.00032 | No Data | 1,200 | 6,100 | 12,000 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.016 | 0.0032 | 0.0016 | No Data | **240** | 1,200 | 2,400 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.0073 | 0.001465 | 0.00073 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.0046 | 0.00092 | 0.00046 | No Data | 860 | 4,300 | 8,600 | No Data |
| (6c) RTU Pet Collars - 99/1 liquid/dust ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 0.000073 | 0.000015 | 0.0000073 | No Data | 54,000 | 270,000 | 540,000 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 0.00012 | 0.000025 | 0.000012 | No Data | 32,000 | 160,000 | 320,000 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 0.00020 | 0.000041 | 0.000020 | No Data | 19,000 | 97,000 | 190,000 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 0.000097 | 0.000019 | 0.000010 | No Data | 40,000 | 200,000 | 400,000 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 0.00011 | 0.000022 | 0.000011 | No Data | 35,000 | 180,000 | 350,000 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 0.000079 | 0.000016 | 0.0000079 | No Data | 50,000 | 250,000 | 500,000 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Inhalation Dose (mg/kg/day) | | | | Inhalation MOEs (LOC is an MOE = 300) For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | No R | PF5 R | PF10 R | EC | No R | PF5 R | PF10 R | EC |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 0.00016 | 0.000033 | 0.000016 | No Data | 24,000 | 120,000 | 240,000 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 0.00012 | 0.000025 | 0.000012 | No Data | 32,000 | 160,000 | 320,000 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 0.00020 | 0.000041 | 0.000020 | No Data | 19,000 | 97,000 | 190,000 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 0.000065 | 0.000013 | 0.0000065 | No Data | 61,000 | 300,000 | 610,000 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 0.00033 | 0.000065 | 0.000033 | No Data | 12,000 | 61,000 | 120,000 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 0.00015 | 0.000029 | 0.000015 | No Data | 27,000 | 130,000 | 270,000 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 0.000091 | 0.000018 | 0.0000091 | No Data | 43,000 | 220,000 | 430,000 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 0.00075 | 0.00015 | 0.000075 | No Data | 5,200 | 26,000 | 52,000 | 5,200 |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 0.0019 | 0.00038 | 0.00019 | No Data | 2,100 | 10,000 | 21,000 | 2,100 |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 0.0030 | 0.00061 | 0.00030 | No Data | 1,300 | 6,500 | 13,000 | 1,300 |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 0.00018 | 0.000037 | 0.000018 | No Data | 22,000 | 110,000 | 220,000 | 22,000 |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 0.00045 | 0.000089 | 0.000045 | No Data | 8,800 | 44,000 | 88,000 | 8,800 |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 0.00069 | 0.00014 | 0.000069 | No Data | 5,700 | 29,000 | 57,000 | 5,700 |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 0.0013 | 0.00025 | 0.00013 | No Data | 3,100 | 16,000 | 31,000 | 3,100 |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | 1,900 |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | No Data |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 0.0043 | 0.00085 | 0.00043 | No Data | 920 | 4,600 | 9,200 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 0.0053 | 0.0011 | 0.00053 | No Data | 750 | 3,700 | 7,500 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 0.0022 | 0.00045 | 0.00022 | No Data | 1,800 | 8,800 | 18,000 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 0.0057 | 0.0011 | 0.00057 | No Data | 690 | 3,500 | 6,900 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 0.0091 | 0.0018 | 0.00091 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 0.00057 | 0.00011 | 0.000057 | No Data | 6,900 | 35,000 | 69,000 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 0.0014 | 0.00027 | 0.00014 | No Data | 2,900 | 14,000 | 29,000 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 0.0020 | 0.00041 | 0.00020 | No Data | 1,900 | 9,700 | 19,000 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 0.00021 | 0.000042 | 0.000021 | No Data | 19,000 | 94,000 | 190,000 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 0.00029 | 0.000059 | 0.000029 | No Data | 13,000 | 67,000 | 130,000 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 0.000042 | 0.0000084 | 0.0000042 | No Data | 94,000 | 470,000 | 940,000 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 0.000061 | 0.000012 | 0.0000061 | No Data | 64,000 | 320,000 | 640,000 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 0.00029 | 0.000059 | 0.000029 | No Data | 13,000 | 67,000 | 130,000 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 0.00034 | 0.000067 | 0.000034 | No Data | 12,000 | 58,000 | 120,000 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 0.00057 | 0.00012 | 0.000057 | No Data | 6,900 | 34,000 | 69,000 | No Data |
| **Mixers/Loaders/Applicators** | | | | | | | | | | | |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.0068 | 0.0014 | 0.00068 | No Data | 580 | 2,900 | 5,800 | No Data |
| | | 0.032 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Woody Borders of Kennels, Yards, | 0.032 lb ai/sq ft | 1,000 sq ft | 0.014 | 0.0028 | 0.0014 | No Data | **280** | 1,400 | 2,800 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Campgrounds, Recreational Parks, Footpaths and Roadways | | (spot) | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 0.0045 | 0.00090 | 0.00045 | No Data | 870 | 4,400 | 8,700 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 0.0085 | 0.0017 | 0.00085 | No Data | 460 | 2,300 | 4,600 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 0.00085 | 0.00017 | 0.000085 | No Data | 4,600 | 23,000 | 46,000 | No Data |
| | | 0.0013 lb ai/animal | | 0.00023 | 0.000045 | 0.000023 | No Data | 17,000 | 87,000 | 170,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.0067 | 0.0013 | 0.00067 | No Data | 590 | 2,900 | 5,900 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0011 | 0.00023 | 0.00011 | No Data | 3,500 | 17,000 | 35,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.00068 | 0.00014 | 0.000068 | No Data | 5,800 | 29,000 | 58,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.00056 | 0.00011 | 0.000056 | No Data | 7,100 | 35,000 | 71,000 | No Data |
| (9b) Liquid: Manually-Pressurized Handwand | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.0068 | 0.0014 | 0.00068 | No Data | 580 | 2,900 | 5,800 | No Data |
| | | 0.032 lb ai/animal | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 0.0139 | 0.0028 | 0.0014 | No Data | **280** | 1,400 | 2,800 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Recreational Parks, Footpaths and Roadways | | | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 0.0045 | 0.00090 | 0.00045 | No Data | 870 | 4,400 | 8,700 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 0.0085 | 0.0017 | 0.00085 | No Data | 460 | 2,300 | 4,600 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 0.00085 | 0.00017 | 0.000085 | No Data | 4,600 | 23,000 | 46,000 | No Data |
| | | 0.0013 lb ai/animal | | 0.00023 | 0.00045 | 0.000023 | No Data | 17,000 | 87,000 | 170,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.0067 | 0.0013 | 0.00067 | No Data | 590 | 2,900 | 5,900 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 710 | 3,500 | 7,100 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0028 | 0.00054 | 0.00027 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0011 | 0.00023 | 0.00011 | No Data | 3,500 | 17,000 | 35,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.00068 | 0.00014 | 0.000068 | No Data | 5,800 | 29,000 | 58,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.00056 | 0.00011 | 0.000056 | No Data | 7,100 | 35,000 | 71,000 | No Data |
| (9c) Liquid: Mechanically -Pressurized Handgun | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 0.018 | 0.0036 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | | 0.032 lb ai/animal | | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, | 0.026 lb ai/animal | | 0.012 | 0.0024 | 0.0012 | No Data | 330 | 1,700 | 3,300 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Footpaths and Roadways | | | | | | | | | | |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 0.023 | 0.0045 | 0.0023 | No Data | **180** | 880 | 1,800 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 0.0023 | 0.00045 | 0.00023 | No Data | 1,800 | 8,800 | 18,000 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 0.00060 | 0.00012 | 0.000060 | No Data | 6,600 | 33,000 | 66,000 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 0.018 | 0.0035 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 0.0073 | 0.0015 | 0.00073 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 0.0030 | 0.00060 | 0.00023 | No Data | 1,300 | 6,600 | 13,000 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 0.0018 | 0.00036 | 0.00018 | No Data | 2,200 | 11,000 | 22,000 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 0.0015 | 0.00029 | 0.00015 | No Data | 2,700 | 13,000 | 27,000 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 (gallons/ day) | 1.2E-05 | 2.5E-06 | 1.2E-06 | No Data | 320,000 | 1,600,000 | 3,200,000 | No Data |
| | | 0.064 lb ai/gallon | | 1.0E-05 | 2.0E-06 | 1.0E-06 | No Data | 390,000 | 1,900,000 | 3,900,000 | No Data |
| (10a) Wettable Powder: Backpack Sprayer | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Poultry (Floor Management Litter, | 0.00080 lb ai/sq ft | 20,000 sq ft | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | | 0.0014 | 0.00028 | 0.00014 | No Data | 2,800 | 14,000 | 28,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 0.00070 | 0.00014 | 0.000070 | No Data | 5,700 | 28,000 | 57,000 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 0.000017 | 0.0000035 | 0.0000017 | No Data | 230,000 | 1,100,000 | 2,300,000 | No Data |
| (10b) Wettable Powder: Manually-Pressurized Handwand | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure | 0.00080 lb ai/sq ft | 20,000 sq ft | 0.0070 | 0.0014 | 0.00070 | No Data | 570 | 2,800 | 5,700 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 0.0035 | 0.00070 | 0.00035 | No Data | 1,100 | 5,700 | 11,000 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 0.0028 | 0.00056 | 0.00028 | No Data | 1,400 | 7,100 | 14,000 | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0014 | 0.00028 | 0.00014 | No Data | 2,800 | 14,000 | 28,000 | No Data |
| | | 0.000080 lb ai/sq ft | | 0.00070 | 0.00014 | 0.000070 | No Data | 5,700 | 28,000 | 57,000 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 0.000017 | 0.0000035 | 0.0000017 | No Data | 230,000 | 1,100,000 | 2,300,000 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 4.13 | 0.828 | 0.413 | No Data | **1** | **5** | **10** | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 10.10 | 2.010 | 1.010 | No Data | **0** | **2** | **4** | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 2.97 | 0.594 | 0.297 | No Data | **1** | **7** | **13** | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - Plunger Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 0.11 | 0.023 | 0.011 | No Data | **35** | **180** | 350 | No Data |
| (10f) Wettable Powder: Plunger | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 0.039 | 0.0078 | 0.0039 | No Data | **100** | 500 | 1,000 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 0.019 | 0.0038 | 0.0019 | No Data | **210** | 1,000 | 2,100 | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| Duster (Dust Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 0.0056 | 0.0011 | 0.00056 | No Data | 700 | 3,500 | 7,000 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 0.18 | 0.037 | 0.018 | No Data | **21** | **110** | **210** | No Data |
| | | 0.38 lb ai/dust bag | | 0.093 | 0.019 | 0.0093 | No Data | **42** | **210** | 420 | No Data |
| | | 0.13 lb ai/dust bag | | 0.032 | 0.0064 | 0.0032 | No Data | **120** | 620 | 1,200 | No Data |
| (11b) Dust: Shaker Can | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 0.76 | 0.15 | 0.076 | No Data | **5** | **26** | **52** | No Data |
| | | 0.0038 lb ai/animal | | 0.39 | 0.077 | 0.039 | No Data | **10** | **51** | **100** | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 0.13 | 0.026 | 0.013 | No Data | **30** | **150** | 300 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/ bird | 1,000 birds | 0.15 | 0.030 | 0.015 | No Data | **26** | **130** | **260** | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 0.076 | 0.015 | 0.0076 | No Data | **52** | **260** | 520 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 0.051 | 0.010 | 0.0051 | No Data | **78** | 390 | 780 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/ bird | 1,000 birds | 0.025 | 0.0051 | 0.0025 | No Data | **160** | 780 | 1,600 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 0.074 | 0.015 | 0.0074 | No Data | **54** | **270** | 540 | No Data |
| | | 0.0038 lb ai/animal | | 0.037 | 0.0075 | 0.0037 | No Data | **110** | 530 | 1,100 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 0.013 | 0.0026 | 0.0013 | No Data | 310 | 1,500 | 3,100 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 0.29 | 0.060 | 0.029 | No Data | **13** | **67** | **130** | No Data |

| Table K.1. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 0.15 | 0.029 | 0.015 | No Data | **27** | **130** | **270** | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 0.049 | 0.0098 | 0.0049 | No Data | **80** | 400 | 800 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 0.015 | 0.0029 | 0.0015 | No Data | **270** | 1,300 | 2,700 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/ sq ft | 1,000 sq ft | 0.0074 | 0.0015 | 0.00074 | No Data | 540 | 2,700 | 5,400 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 0.0025 | 0.00049 | 0.00025 | No Data | 1,600 | 8,000 | 16,000 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 0.00065 | 0.00013 | 0.000065 | No Data | 6,100 | 30,000 | 61,000 | No Data |
| | | 0.077 lb ai/gallon | | 0.00063 | 0.00013 | 0.000063 | No Data | 6,300 | 32,000 | 63,000 | No Data |
| | | 0.064 lb ai/gallon | | 0.00052 | 0.00010 | 0.000052 | No Data | 7,600 | 38,000 | 76,000 | No Data |
| | | 0.03 lb ai/gallon | | 0.00024 | 0.000049 | 0.000024 | No Data | 16,000 | 81,000 | 160,000 | No Data |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 0.0013 | 0.00026 | 0.00013 | No Data | 3,000 | 15,000 | 30,000 | No Data |
| | | 0.077 lb ai/gallon | | 0.0013 | 0.00025 | 0.00013 | No Data | 3,200 | 16,000 | 32,000 | No Data |
| | | 0.064 lb ai/gallon | | 0.0010 | 0.00021 | 0.00010 | No Data | 3,800 | 19,000 | 38,000 | No Data |
| | | 0.03 lb ai/gallon | | 0.00049 | 0.000097 | 0.000049 | No Data | 8,100 | 40,000 | 81,000 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 0.00014 | 0.000027 | 0.000014 | No Data | 29,000 | 140,000 | 290,000 | No Data |
| | | 0.00077 lb ai/animal | | 0.000070 | 0.000014 | 0.0000070 | No Data | 57,000 | 280,000 | 570,000 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 0.00040 | 0.000080 | 0.000040 | No Data | 9,900 | 49,000 | 99,000 | No Data |
| | | 0.0017 lb ai/animal | | 0.00031 | 0.000062 | 0.000031 | No Data | 13,000 | 64,000 | 130,000 | No Data |

| Table K.2. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0070 | No Data | No Data | No Data | 570 | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/ sq ft | 100,000 sq ft | 0.035 | No Data | No Data | No Data | **110** | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.014 | No Data | No Data | No Data | **280** | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0070 | No Data | No Data | No Data | 570 | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | 0.0035 | No Data | No Data | No Data | 1,100 | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.0016 | No Data | No Data | No Data | 2,400 | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.00081 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.0081 | No Data | No Data | No Data | 490 | No Data | No Data | No Data |

| Table K.2. TCVP Occupational Handler Non-Cancer Risk Estimates. | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Inhalation Dose (mg/kg/day)** | | | | **Inhalation MOEs (LOC is an MOE = 300)** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | |
| | | | | **No R** | **PF5 R** | **PF10 R** | **EC** | **No R** | **PF5 R** | **PF10 R** | **EC** |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.00081 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.0033 | No Data | No Data | No Data | 1,200 | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | 0.0016 | No Data | No Data | No Data | 2,400 | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | 0.000812 | No Data | No Data | No Data | 4,900 | No Data | No Data | No Data |
| **Mixer/Loader/Applicators** | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 0.018 | 0.0037 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 100,000 sq ft | 0.092 | 0.018 | 0.0092 | No Data | **43** | **220** | 430 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/birds | 20,000 birds | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 100,000 sq ft | 0.037 | 0.0073 | 0.0037 | No Data | **110** | 540 | 1,100 | No Data |
| | | 0.00016 lb ai/sq ft | | 0.018 | 0.0037 | 0.0018 | No Data | **220** | 1,100 | 2,200 | No Data |
| | | 0.000080 lb ai/sq ft | | 0.0092 | 0.0018 | 0.00092 | No Data | 430 | 2,200 | 4,300 | No Data |

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## Appendix L. Summary of Occupational Handler Cancer Risk Estimates

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | 100,000 sq ft | 5E-07 | 9E-08 | 7E-08 | 5E-07 | 9E-08 | 7E-08 | 5E-07 | 9E-08 | 7E-08 | 2E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 4E-07 | 8E-08 | 6E-08 | 4E-07 | 8E-08 | 6E-08 | 4E-07 | 7E-08 | 6E-08 | 2E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 9E-08 | 2E-08 | 1E-08 | 9E-08 | 2E-08 | 1E-08 | 9E-08 | 2E-08 | 1E-08 | 4E-09 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 7E-09 | 6E-09 | 2E-09 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 1E-09 | 2E-10 | 1E-10 | 1E-09 | 2E-10 | 1E-10 | 1E-09 | 2E-10 | 1E-10 | 5E-11 |
| | | 0.064 lb ai/gallon | | 9E-10 | 2E-10 | 1E-10 | 9E-10 | 2E-10 | 1E-10 | 9E-10 | 1E-10 | 1E-10 | 4E-11 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 1E-05 | 2E-06 | 1E-06 | 9E-06 | 6E-07 | 5E-07 | 9E-06 | 5E-07 | 4E-07 | 3E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/ sq ft | | 4E-06 | 6E-07 | 6E-07 | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 2E-07 | 2E-07 | 1E-08 |
| (2b) Mixing/ Loading Wettable Powders for | Poultry (Floor Management – Roost) | 0.080 lb ai/gallon | 2 gallons | 8E-09 | 1E-09 | 1E-09 | 7E-09 | 5E-10 | 4E-10 | 7E-09 | 4E-10 | 3E-10 | 2E-11 |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Paint Applications | | | | | | | | | | | | | |
| (3a) Mixing/ Loading Dusts for Paint Applications (WP Data as Surrogate) | | 0.030 lb ai/gallon | | 8E-09 | 1E-09 | 1E-09 | 7E-09 | 5E-10 | 4E-10 | 7E-09 | 4E-10 | 3E-10 | 2E-11 |
| **Applicators** | | | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 4E-08 | 3E-08 | 1E-08 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 4E-08 | 3E-08 | 1E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 2E-07 | 4E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 1E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 8E-08 | 2E-08 | 2E-08 | 8E-08 | 2E-08 | 1E-08 | 8E-08 | 2E-08 | 1E-08 | 5E-09 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 3E-08 | 8E-09 | 6E-09 | 3E-08 | 7E-09 | 5E-09 | 3E-08 | 7E-09 | 5E-09 | 2E-09 |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 3E-09 | 3E-09 | 1E-09 |
| | Cattle Feed | 0.0039 | 1,000 | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 3E-09 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (5) Open Pour Liquid Additive for Feed Through Applications | (Concentrate) | lb ai/animal | cows | | | | | | | | | | |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 2E-08 | 3E-09 | 2E-09 | 1E-08 | 3E-09 | 2E-09 | 1E-08 | 3E-09 | 2E-09 | No Data |
| | Horse Feed | 0.0017 lb ai/animal | 500 horses | 6E-09 | 1E-09 | 8E-10 | 6E-09 | 1E-09 | 8E-10 | 6E-09 | 1E-09 | 8E-10 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 4E-09 | 3E-09 | 3E-08 | 4E-09 | 3E-09 | No Data |
| (6a) RTU Pet Collar Applications – 1/99 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 1E-07 | 1E-07 | 4E-06 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 6E-06 | 4E-07 | 4E-07 | 6E-06 | 2E-07 | 2E-07 | 6E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 6E-06 | 4E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 4E-06 | 3E-07 | 2E-07 | 4E-06 | 1E-07 | 1E-07 | 4E-06 | 1E-07 | 9E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 8E-06 | 6E-07 | 5E-07 | 8E-06 | 3E-07 | 2E-07 | 8E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 6E-06 | 4E-07 | 4E-07 | 6E-06 | 2E-07 | 2E-07 | 6E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 9E-08 | 3E-06 | 1E-07 | 7E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 6E-07 | 4E-07 | 2E-05 | 5E-07 | 4E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 7E-06 | 5E-07 | 4E-07 | 7E-06 | 3E-07 | 2E-07 | 7E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 1E-07 | 1E-07 | No Data |
| (6b) RTU Pet Collar | Cat (2596-49) | 0.0036 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 1E-07 | 7E-08 | 2E-06 | 9E-08 | 6E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Applications – 50/50 Liquid/Dust Ratio | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 3E-06 | 3E-07 | 2E-07 | 3E-06 | 2E-07 | 1E-07 | 3E-06 | 1E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 2E-06 | 1E-07 | 9E-08 | 2E-06 | 1E-07 | 8E-08 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 1E-07 | 3E-06 | 1E-07 | 9E-08 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 1E-07 | 7E-08 | 2E-06 | 9E-08 | 6E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 4E-06 | 4E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 3E-06 | 3E-07 | 2E-07 | 3E-06 | 2E-07 | 1E-07 | 3E-06 | 1E-07 | 1E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 2E-06 | 1E-07 | 1E-07 | 2E-06 | 8E-08 | 6E-08 | 2E-06 | 8E-08 | 5E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 9E-06 | 7E-07 | 6E-07 | 8E-06 | 4E-07 | 3E-07 | 8E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 4E-06 | 3E-07 | 3E-07 | 4E-06 | 2E-07 | 1E-07 | 4E-06 | 2E-07 | 1E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 2E-06 | 2E-07 | 2E-07 | 2E-06 | 1E-07 | 8E-08 | 2E-06 | 1E-07 | 7E-08 | No Data |
| (6c) RTU Pet Collar Applications – 99/1 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 1E-07 | 6E-08 | 4E-08 | 1E-07 | 6E-08 | 4E-08 | 1E-07 | 6E-08 | 4E-08 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 2E-07 | 1E-07 | 7E-08 | 2E-07 | 1E-07 | 6E-08 | 2E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 6E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 1E-07 | 7E-08 | 4E-08 | 1E-07 | 7E-08 | 4E-08 | 1E-07 | 7E-08 | 4E-08 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 3E-07 | 1E-07 | 9E-08 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 2E-07 | 1E-07 | 7E-08 | 2E-07 | 1E-07 | 6E-08 | 2E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 1E-07 | 6E-08 | 3E-08 | 1E-07 | 5E-08 | 3E-08 | 1E-07 | 5E-08 | 3E-08 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | 2E-07 | 8E-08 | 5E-08 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 4E-07 | 3E-08 | 2E-08 | 4E-07 | 1E-08 | 1E-08 | 4E-07 | 1E-08 | 8E-09 | No Data |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 9E-07 | 3E-08 | 3E-08 | 9E-07 | 3E-08 | 2E-08 | No Data |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 2E-06 | 1E-07 | 9E-08 | 2E-06 | 5E-08 | 4E-08 | 2E-06 | 5E-08 | 3E-08 | No Data |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 9E-08 | 6E-09 | 6E-09 | 9E-08 | 3E-09 | 2E-09 | 9E-08 | 3E-09 | 2E-09 | No Data |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 2E-07 | 2E-08 | 1E-08 | 2E-07 | 8E-09 | 6E-09 | 2E-07 | 7E-09 | 5E-09 | No Data |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 4E-07 | 2E-08 | 2E-08 | 3E-07 | 1E-08 | 9E-09 | 3E-07 | 1E-08 | 8E-09 | No Data |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 6E-07 | 4E-08 | 4E-08 | 6E-07 | 2E-08 | 2E-08 | 6E-07 | 2E-08 | 1E-08 | No Data |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 2E-06 | 2E-07 | 1E-07 | 2E-06 | 8E-08 | 6E-08 | 2E-06 | 7E-08 | 5E-08 | No Data |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 9E-08 | 7E-08 | 3E-06 | 8E-08 | 6E-08 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 1E-06 | 8E-08 | 7E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 3E-06 | 2E-07 | 2E-07 | 3E-06 | 1E-07 | 8E-08 | 3E-06 | 9E-08 | 6E-08 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 5E-06 | 3E-07 | 3E-07 | 5E-06 | 2E-07 | 1E-07 | 5E-06 | 1E-07 | 1E-07 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 3E-07 | 2E-08 | 2E-08 | 3E-07 | 1E-08 | 8E-09 | 3E-07 | 9E-09 | 6E-09 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 7E-07 | 5E-08 | 4E-08 | 7E-07 | 2E-08 | 2E-08 | 7E-07 | 2E-08 | 2E-08 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 1E-06 | 7E-08 | 6E-08 | 1E-06 | 4E-08 | 3E-08 | 1E-06 | 3E-08 | 2E-08 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 8E-08 | 7E-08 | 4E-08 | 7E-08 | 7E-08 | 4E-08 | 7E-08 | 7E-08 | 4E-08 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 5E-08 | 1E-07 | 1E-07 | 5E-08 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 2E-08 | 1E-08 | 8E-09 | 1E-08 | 1E-08 | 8E-09 | 1E-08 | 1E-08 | 7E-09 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 2E-08 | 2E-08 | 1E-08 | 2E-08 | 2E-08 | 1E-08 | 2E-08 | 2E-08 | 1E-08 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 5E-08 | 1E-07 | 1E-07 | 5E-08 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 1E-07 | 1E-07 | 7E-08 | 1E-07 | 1E-07 | 6E-08 | 1E-07 | 1E-07 | 6E-08 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| Mixers/Loaders/Applicators | | | | | | | | | | | | | |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | | 0.032 lb ai/animal | | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 7E-07 | 1E-06 | 1E-06 | 6E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 2E-06 | 2E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 9E-07 | 9E-07 | 6E-07 | 8E-07 | 8E-07 | 5E-07 | 8E-07 | 8E-07 | 5E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| | | 0.0013 lb ai/animal | | 5E-08 | 5E-08 | 3E-08 | 4E-08 | 4E-08 | 3E-08 | 4E-08 | 4E-08 | 3E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 7E-07 | 1E-06 | 1E-06 | 6E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 6E-07 | 6E-07 | 4E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-07 | 2E-07 | 2E-07 | 2E-07 | 2E-07 | 1E-07 | 2E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 7E-08 | 1E-07 | 1E-07 | 6E-08 | No Data |
| (9b) Liquid: Manually-Pressurized Handwand | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | | 0.032 lb ai/animal | | 4E-05 | 3E-07 | 3E-07 | 4E-05 | 2E-07 | 2E-07 | 4E-05 | 2E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 1E-04 | 7E-07 | 7E-07 | 1E-04 | 5E-07 | 4E-07 | 1E-04 | 5E-07 | 4E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 3E-05 | 2E-07 | 2E-07 | 3E-05 | 2E-07 | 1E-07 | 3E-05 | 1E-07 | 1E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 6E-06 | 4E-08 | 4E-08 | 6E-06 | 3E-08 | 3E-08 | 6E-06 | 3E-08 | 2E-08 | No Data |
| | | 0.0013 lb ai/animal | | 2E-06 | 1E-08 | 1E-08 | 2E-06 | 8E-09 | 7E-09 | 2E-06 | 7E-09 | 6E-09 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 4E-05 | 3E-07 | 3E-07 | 4E-05 | 2E-07 | 2E-07 | 4E-05 | 2E-07 | 2E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 8E-08 | 2E-05 | 9E-08 | 8E-08 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 8E-06 | 6E-08 | 5E-08 | 8E-06 | 4E-08 | 3E-08 | 8E-06 | 4E-08 | 3E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 4E-06 | 3E-08 | 3E-08 | 4E-06 | 2E-08 | 2E-08 | 4E-06 | 2E-08 | 2E-08 | No Data |
| (9c) Liquid: Mechanically -Pressurized Handgun | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 1E-06 | 7E-07 | 6E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 3E-07 | 2E-07 | No Data |
| | | 0.032 lb ai/animal | | 1E-06 | 6E-07 | 5E-07 | 8E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.026 lb ai/animal | | 8E-07 | 5E-07 | 4E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 2E-07 | 1E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 2E-06 | 9E-07 | 7E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 4E-07 | 3E-07 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 2E-07 | 9E-08 | 7E-08 | 1E-07 | 5E-08 | 3E-08 | 1E-07 | 4E-08 | 3E-08 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 4E-08 | 2E-08 | 2E-08 | 3E-08 | 1E-08 | 8E-09 | 3E-08 | 1E-08 | 7E-09 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-06 | 7E-07 | 6E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 3E-07 | 2E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 6E-07 | 5E-07 | 8E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 5E-07 | 3E-07 | 2E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 1E-07 | 9E-08 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-07 | 1E-07 | 9E-08 | 2E-07 | 6E-08 | 4E-08 | 2E-07 | 6E-08 | 4E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-07 | 7E-08 | 6E-08 | 9E-08 | 4E-08 | 3E-08 | 9E-08 | 3E-08 | 2E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-07 | 6E-08 | 5E-08 | 8E-08 | 3E-08 | 2E-08 | 7E-08 | 3E-08 | 2E-08 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 (gallons/ day) | 3E-08 | 5E-09 | 4E-09 | 3E-08 | 5E-09 | 3E-09 | 3E-08 | 5E-09 | 3E-09 | No Data |
| | | 0.064 lb ai/gallon | | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 4E-09 | 3E-09 | 2E-08 | 4E-09 | 3E-09 | No Data |
| (10a) Wettable | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Powder: Backpack Sprayer | Swine - Direct Spray | 0.020 lb ai/animal | | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 1E-06 | 1E-06 | 9E-07 | 1E-06 | 1E-06 | 8E-07 | 1E-06 | 1E-06 | 8E-07 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/ sq ft | | 6E-07 | 6E-07 | 4E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | 20,000 sq ft | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 2E-07 | 2E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 3E-09 | 3E-09 | 2E-09 | 3E-09 | 3E-09 | 2E-09 | 3E-09 | 3E-09 | 2E-09 | No Data |
| (10b) Wettable Powder: Manually-Pressurized Handwand | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 1E-07 | No Data |
| | Poultry (Floor Management Litter, | 0.00080 lb ai/sq ft | 20,000 sq ft | 5E-05 | 4E-07 | 3E-07 | 5E-05 | 2E-07 | 2E-07 | 5E-05 | 2E-07 | 2E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | | | | | | | | | | | | |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 1E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 8E-08 | 2E-05 | 9E-08 | 8E-08 | No Data |
| | | 0.00016 lb ai/sq ft | | 1E-05 | 7E-08 | 7E-08 | 1E-05 | 5E-08 | 4E-08 | 1E-05 | 5E-08 | 4E-08 | No Data |
| | | 0.000080 lb ai/sq ft | | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 1E-07 | 9E-10 | 8E-10 | 1E-07 | 6E-10 | 5E-10 | 1E-07 | 6E-10 | 5E-10 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 9E-05 | 9E-05 | 9E-05 | 2E-05 | 2E-05 | 2E-05 | 9E-06 | 9E-06 | 9E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 2E-04 | 2E-04 | 2E-04 | 4E-05 | 4E-05 | 4E-05 | 2E-05 | 2E-05 | 2E-05 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 7E-05 | 7E-05 | 7E-05 | 1E-05 | 1E-05 | 1E-05 | 7E-06 | 7E-06 | 7E-06 | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - Plunger Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| (10f) Wettable Powder: Plunger | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 9E-06 | 2E-06 | 2E-06 | 8E-06 | 1E-06 | 1E-06 | 8E-06 | 1E-06 | 1E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 4E-06 | 1E-06 | 9E-07 | 4E-06 | 7E-07 | 6E-07 | 4E-06 | 6E-07 | 5E-07 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Duster (Dust Data as Surrogate) | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 1E-06 | 3E-07 | 3E-07 | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 4E-05 | 1E-05 | 9E-06 | 4E-05 | 7E-06 | 6E-06 | 4E-05 | 6E-06 | 5E-06 | No Data |
| | | 0.38 lb ai/dust bag | | 2E-05 | 5E-06 | 4E-06 | 2E-05 | 3E-06 | 3E-06 | 2E-05 | 3E-06 | 3E-06 | No Data |
| | | 0.13 lb ai/dust bag | | 7E-06 | 2E-06 | 2E-06 | 7E-06 | 1E-06 | 1E-06 | 7E-06 | 1E-06 | 9E-07 | No Data |
| (11b) Dust: Shaker Can | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 4E-04 | 3E-05 | 2E-05 | 4E-04 | 1E-05 | 1E-05 | 4E-04 | 1E-05 | 8E-06 | No Data |
| | | 0.0038 lb ai/animal | | 2E-04 | 1E-05 | 1E-05 | 2E-04 | 7E-06 | 5E-06 | 2E-04 | 6E-06 | 4E-06 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 7E-05 | 5E-06 | 4E-06 | 7E-05 | 2E-06 | 2E-06 | 6E-05 | 2E-06 | 1E-06 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 8E-05 | 5E-06 | 5E-06 | 8E-05 | 3E-06 | 2E-06 | 8E-05 | 2E-06 | 2E-06 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 4E-05 | 3E-06 | 2E-06 | 4E-05 | 1E-06 | 1E-06 | 4E-05 | 1E-06 | 8E-07 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 9E-07 | 7E-07 | 3E-05 | 8E-07 | 6E-07 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 1E-05 | 9E-07 | 8E-07 | 1E-05 | 5E-07 | 3E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | | 0.0038 lb ai/animal | | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |

| Table L.1. TCVP Occupational Handler Cancer Risk Estimates – Private/ Farmer | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 6E-04 | 9E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | 6E-04 | 8E-05 | 7E-05 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 1E-05 | 2E-06 | 1E-06 | 1E-05 | 2E-06 | 1E-06 | 1E-05 | 2E-06 | 1E-06 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 3E-04 | 4E-05 | 4E-05 | 3E-04 | 4E-05 | 3E-05 | 3E-04 | 4E-05 | 3E-05 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | No Data |
| | | 0.077 lb ai/gallon | | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | 9E-07 | 1E-07 | 1E-07 | No Data |
| | | 0.064 lb ai/gallon | | 7E-08 | 1E-08 | 1E-08 | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | No Data |
| | | 0.03 lb ai/gallon | | 3E-07 | 5E-08 | 5E-08 | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 4E-08 | 4E-08 | No Data |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 2E-07 | 9E-08 | 8E-08 | 2E-07 | 6E-08 | 6E-08 | 2E-07 | 6E-08 | 6E-08 | No Data |
| | | 0.077 lb ai/gallon | | 2E-07 | 8E-08 | 8E-08 | 2E-07 | 6E-08 | 6E-08 | 2E-07 | 6E-08 | 5E-08 | No Data |
| | | 0.064 lb ai/gallon | | 2E-08 | 7E-09 | 6E-09 | 2E-08 | 5E-09 | 5E-09 | 2E-08 | 5E-09 | 4E-09 | No Data |
| | | 0.03 lb ai/gallon | | 9E-08 | 3E-08 | 3E-08 | 8E-08 | 2E-08 | 2E-08 | 8E-08 | 2E-08 | 2E-08 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 1E-09 | 7E-10 | 7E-10 | 6E-10 | 2E-10 | 2E-10 | 6E-10 | 1E-10 | 1E-10 | No Data |
| | | 0.00077 lb ai/animal | | 6E-10 | 3E-10 | 3E-10 | 3E-10 | 9E-11 | 9E-11 | 3E-10 | 6E-11 | 6E-11 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 2E-08 | 1E-08 | 1E-08 | 9E-09 | 3E-09 | 3E-09 | 8E-09 | 2E-09 | 2E-09 | No Data |
| | | 0.0017 lb ai/animal | | 1E-08 | 7E-09 | 7E-09 | 7E-09 | 2E-09 | 2E-09 | 7E-09 | 1E-09 | 1E-09 | No Data |

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| Table L.2. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Private/Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Private/Farmer For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 3E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 3E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 | 20,000 birds | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00032 | 20,000 | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.2. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Private/Farmer | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Private/Farmer** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | lb ai/sq ft | sq ft | | | | | | | | | | |
| | | 0.00016 lb ai/sq ft | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 2E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Mixer/Loader/Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-06 | 7E-07 | 6E-07 | 1E-06 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 2E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 6E-06 | 4E-06 | 3E-06 | 5E-06 | 2E-06 | 1E-06 | 5E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 | 20,000 birds | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 3E-06 | 1E-06 | 1E-06 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 7E-07 | 4E-07 | No Data |
| | | 0.00016 lb ai/sq ft | | 1E-06 | 7E-07 | 6E-07 | 1E-06 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 2E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (1a) Mixing/ Loading Liquids for Groundboom Applications | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | 100,000 (sq ft/day) | 2E-06 | 3E-07 | 2E-07 | 2E-06 | 3E-07 | 2E-07 | 2E-06 | 3E-07 | 2E-07 | 7E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | 1E-06 | 2E-07 | 2E-07 | 6E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 5E-08 | 4E-08 | 3E-07 | 5E-08 | 4E-08 | 1E-08 |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | | 1E-07 | 2E-08 | 2E-08 | 1E-07 | 2E-08 | 2E-08 | 1E-07 | 2E-08 | 2E-08 | 6E-09 |
| (1b) Mixing/ Loading Liquids for Paint Applications | Poultry Buildings (Roost) | 0.077 lb ai/gallon | 2 gallons | 3E-09 | 6E-10 | 4E-10 | 3E-09 | 5E-10 | 4E-10 | 3E-09 | 5E-10 | 4E-10 | 1E-10 |
| | | 0.064 lb ai/gallon | | 3E-09 | 5E-10 | 4E-10 | 3E-09 | 5E-10 | 3E-10 | 3E-09 | 4E-10 | 3E-10 | 1E-10 |
| (2a) Mixing/ Loading Wettable Powders for Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 2E-06 | 1E-06 | 9E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 1E-05 | 2E-06 | 2E-06 | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 6E-07 | 5E-07 | 4E-08 |
| (2b) Mixing/ Loading | | 0.080 lb ai/gallon | 2 gallons | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 1E-09 | 1E-09 | 2E-08 | 1E-09 | 1E-09 | 7E-11 |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Wettable Powders for Paint Applications | Poultry (Floor Management – Roost) | | | | | | | | | | | | |
| (3a) Mixing/ Loading Dusts for Paint Applications (WP Data as Surrogate) | | 0.030 lb ai/gallon | | 2E-08 | 3E-09 | 3E-09 | 2E-08 | 1E-09 | 1E-09 | 2E-08 | 1E-09 | 1E-09 | 7E-11 |
| **Applicators** | | | | | | | | | | | | | |
| (4) Groundboom Applications | Poultry Buildings (Including: Droppings, Floor Management Litter, Fowl Tick, Garbage Piles, Manure Piles, Under Feed Troughs) | 0.00080 lb ai/sq ft | 100,000 sq ft | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 1E-07 | 4E-08 |
| | Poultry Buildings (Including: Ceilings, Floors, Larvicide, Walls) | 0.00077 lb ai/sq ft | | 6E-07 | 1E-07 | 1E-07 | 6E-07 | 1E-07 | 9E-08 | 6E-07 | 1E-07 | 9E-08 | 4E-08 |
| | Poultry Buildings (Including: Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 5E-07 | 1E-07 | 1E-07 | 5E-07 | 1E-07 | 8E-08 | 5E-07 | 1E-07 | 8E-08 | 3E-08 |
| | Dairy Barns, Poultry Houses, Swine Barns, or Other Animal Buildings | 0.00032 lb ai/sq ft | | 2E-07 | 6E-08 | 5E-08 | 2E-07 | 5E-08 | 4E-08 | 2E-07 | 5E-08 | 4E-08 | 2E-08 |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | | 1E-07 | 2E-08 | 2E-08 | 9E-08 | 2E-08 | 2E-08 | 9E-08 | 2E-08 | 2E-08 | 7E-09 |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Poultry (Floor Management) | 0.000064 lb ai/sq ft | | 5E-08 | 1E-08 | 1E-08 | 5E-08 | 1E-08 | 8E-09 | 5E-08 | 1E-08 | 8E-09 | 3E-09 |
| (5) Open Pour Liquid Additive for Feed Through Applications | Cattle Feed (Concentrate) | 0.0039 lb ai/animal | 1,000 cows | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| | Cattle Feed (Concentrate) | 0.0022 lb ai/animal | | 5E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | 4E-08 | 8E-09 | 6E-09 | No Data |
| | Horse Feed | 0.0017 lb ai/animal | 500 horses | 2E-08 | 3E-09 | 2E-09 | 2E-08 | 3E-09 | 2E-09 | 2E-08 | 3E-09 | 2E-09 | No Data |
| | Swine Feed | 0.00060 lb ai/animal | 6,250 pigs | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| (6a) RTU Pet Collar Applications – 1/99 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | 8 animals | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 7E-07 | 5E-07 | 2E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 1E-06 | 8E-07 | 3E-05 | 9E-07 | 7E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 1E-05 | 1E-06 | 9E-07 | 1E-05 | 5E-07 | 4E-07 | 1E-05 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 6E-07 | 4E-07 | 2E-05 | 5E-07 | 4E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 1E-05 | 4E-07 | 3E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 2E-05 | 2E-06 | 1E-06 | 2E-05 | 9E-07 | 6E-07 | 2E-05 | 8E-07 | 5E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 7E-07 | 5E-07 | 2E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 3E-05 | 1E-06 | 8E-07 | 3E-05 | 9E-07 | 7E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 1E-05 | 7E-07 | 6E-07 | 9E-06 | 3E-07 | 3E-07 | 9E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 5E-05 | 3E-06 | 3E-06 | 5E-05 | 2E-06 | 1E-06 | 5E-05 | 2E-06 | 1E-06 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 2E-05 | 2E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 1E-05 | 1E-06 | 8E-07 | 1E-05 | 5E-07 | 4E-07 | 1E-05 | 4E-07 | 3E-07 | No Data |
| (6b) RTU Pet Collar Applications - 50/50 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 6E-06 | 5E-07 | 4E-07 | 6E-06 | 3E-07 | 2E-07 | 6E-06 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 9E-06 | 5E-07 | 3E-07 | 9E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 8E-06 | 6E-07 | 5E-07 | 7E-06 | 4E-07 | 3E-07 | 7E-06 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 9E-06 | 7E-07 | 6E-07 | 9E-06 | 4E-07 | 3E-07 | 8E-06 | 4E-07 | 3E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 6E-06 | 5E-07 | 4E-07 | 6E-06 | 3E-07 | 2E-07 | 6E-06 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 1E-05 | 1E-06 | 9E-07 | 1E-05 | 6E-07 | 4E-07 | 1E-05 | 6E-07 | 4E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 1E-05 | 8E-07 | 7E-07 | 9E-06 | 5E-07 | 3E-07 | 9E-06 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 2E-05 | 1E-06 | 1E-06 | 2E-05 | 8E-07 | 6E-07 | 2E-05 | 7E-07 | 5E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 5E-06 | 4E-07 | 4E-07 | 5E-06 | 3E-07 | 2E-07 | 5E-06 | 2E-07 | 2E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 3E-05 | 2E-06 | 2E-06 | 2E-05 | 1E-06 | 9E-07 | 2E-05 | 1E-06 | 8E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 1E-05 | 1E-06 | 8E-07 | 1E-05 | 6E-07 | 4E-07 | 1E-05 | 5E-07 | 4E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 7E-06 | 6E-07 | 5E-07 | 7E-06 | 4E-07 | 3E-07 | 7E-06 | 3E-07 | 2E-07 | No Data |
| (6c) RTU Pet Collar Applications - 99/1 Liquid/Dust Ratio | Cat (2596-49) | 0.0036 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-50,62) - Small | 0.0061 lb ai/animal | | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-50,62) - Large | 0.010 lb ai/animal | | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-63) - Small | 0.0048 lb ai/animal | | 5E-07 | 2E-07 | 2E-07 | 5E-07 | 2E-07 | 2E-07 | 5E-07 | 2E-07 | 2E-07 | No Data |
| | Cat (2596-63) - Large | 0.0055 lb ai/animal | | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | 6E-07 | 3E-07 | 2E-07 | No Data |
| | Cat (2596-83) - Small | 0.0039 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Cat (2596-83) - Large | 0.0080 lb ai/animal | | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 3E-07 | 9E-07 | 4E-07 | 3E-07 | No Data |
| | Dog (2596-84) – Small | 0.0061 lb ai/animal | | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | 7E-07 | 3E-07 | 2E-07 | No Data |
| | Dog (2596-84) – Large | 0.010 lb ai/animal | | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-139) - All | 0.0032 lb ai/animal | | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | 4E-07 | 2E-07 | 1E-07 | No Data |
| | Dog (2596-139) - All | 0.016 lb ai/animal | | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 8E-07 | 5E-07 | No Data |
| | Dog (11556-164) - All | 0.0072 lb ai/animal | | 8E-07 | 4E-07 | 2E-07 | 8E-07 | 4E-07 | 2E-07 | 8E-07 | 4E-07 | 2E-07 | No Data |
| | Cat (11556-165) - All | 0.0045 lb ai/animal | | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| (7) RTU Dust/Powder Applications | Dog (47000-123) - Small | 0.00037 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (47000-123) - Medium | 0.00094 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (47000-123) - Large | 0.0015 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (47000-123) - Small | 0.000090 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Cat (47000-123) - Medium | 0.00022 lb ai/animal | | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | Cat (47000-123) - Large | 0.00034 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (2596-78) - Small | 0.00062 lb ai/animal | | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Cat (2596-78) - Large | 0.0010 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Dog (2596-79) - Small | 0.0010 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Dog (2596-79) - Medium | 0.0021 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Dog (2596-79) - Large | 0.0026 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (67517-82) - Small | 0.0011 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (67517-82) - Medium | 0.0028 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Dog (67517-82) - Large | 0.0045 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Cat (67517-82) - Small | 0.00028 lb ai/animal | | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | Cat (67517-82) - Medium | 0.00067 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Cat (67517-82) - Large | 0.0010 lb ai/animal | | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |
| (8) RTU Pump/Trigger Spray Applications | Cat (2596-126,140) - Trigger -Small | 0.00055 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Cat (2596-126,140) - Trigger - Large | 0.00077 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Cat (2596-140) - Pump - Small | 0.00011 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | Cat (2596-140) - Pump - Large | 0.00016 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Dog (2596-125,-140) - Small | 0.00077 lb ai/animal | | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Dog (2596-125,-140) - Medium | 0.00088 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Dog (2596-125,-140) - Large | 0.0015 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| Mixers/Loaders/Applicators | | | | | | | | | | | | | |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| (9a) Liquid: Backpack Sprayer | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | 1E-05 | 1E-05 | 6E-06 | No Data |
| | | 0.032 lb ai/animal | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 8E-06 | 8E-06 | 6E-06 | 8E-06 | 8E-06 | 5E-06 | 8E-06 | 7E-06 | 5E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 3E-06 | 3E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | 2E-06 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | 5E-06 | 5E-06 | 3E-06 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | 5E-07 | 5E-07 | 3E-07 | No Data |
| | | 0.0013 lb ai/animal | | 1E-07 | 1E-07 | 9E-08 | 1E-07 | 1E-07 | 8E-08 | 1E-07 | 1E-07 | 8E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) | 0.00077 lb ai/sq ft | 20,000 sq ft | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | 3E-06 | 3E-06 | 2E-06 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 7E-07 | 7E-07 | 5E-07 | 6E-07 | 6E-07 | 4E-07 | 6E-07 | 6E-07 | 4E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 4E-07 | 4E-07 | 3E-07 | 4E-07 | 4E-07 | 2E-07 | 4E-07 | 4E-07 | 2E-07 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | 3E-07 | 3E-07 | 2E-07 | No Data |
| (9b) Liquid: | | 0.039 | 400 | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Manually-Pressurized Handwand | Beef Cattle - Direct Applied | lb ai/animal | animals | | | | | | | | | | |
| | | 0.032 lb ai/animal | | 1E-04 | 9E-07 | 8E-07 | 1E-04 | 6E-07 | 5E-07 | 1E-04 | 5E-07 | 5E-07 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.032 lb ai/sq ft | 1,000 sq ft (spot) | 3E-04 | 2E-06 | 2E-06 | 3E-04 | 1E-06 | 1E-06 | 3E-04 | 1E-06 | 1E-06 | No Data |
| | Beef Cattle - Direct Applied | 0.026 lb ai/animal | 400 animals | 1E-04 | 7E-07 | 7E-07 | 1E-04 | 5E-07 | 4E-07 | 1E-04 | 4E-07 | 4E-07 | No Data |
| | Swine - Direct Applied | 0.049 lb ai/animal | | 2E-04 | 1E-06 | 1E-06 | 2E-04 | 9E-07 | 8E-07 | 2E-04 | 8E-07 | 7E-07 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0049 lb ai/animal | | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 9E-08 | 8E-08 | 2E-05 | 8E-08 | 7E-08 | No Data |
| | | 0.0013 lb ai/animal | | 5E-06 | 4E-08 | 3E-08 | 5E-06 | 2E-08 | 2E-08 | 5E-06 | 2E-08 | 2E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 1E-04 | 9E-07 | 8E-07 | 1E-04 | 6E-07 | 5E-07 | 1E-04 | 5E-07 | 5E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | Poultry Buildings (Flies Residual) - | 0.00013 lb ai/sq ft | 20,000 sq ft | 2E-05 | 2E-07 | 2E-07 | 2E-05 | 1E-07 | 1E-07 | 2E-05 | 1E-07 | 9E-08 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 1E-05 | 1E-07 | 1E-07 | 1E-05 | 7E-08 | 6E-08 | 1E-05 | 7E-08 | 6E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 1E-05 | 9E-08 | 8E-08 | 1E-05 | 6E-08 | 5E-08 | 1E-05 | 5E-08 | 5E-08 | No Data |
| (9c) Liquid: | Beef Cattle - Direct Applied | 0.039 lb ai/animal | 400 animals | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Mechanically -Pressurized Handgun | | 0.032 lb ai/animal | | 3E-06 | 2E-06 | 1E-06 | 2E-06 | 9E-07 | 6E-07 | 2E-06 | 9E-07 | 5E-07 | No Data |
| | Woody Borders of Kennels, Yards, Campgrounds, Recreational Parks, Footpaths and Roadways | 0.026 lb ai/animal | | 3E-06 | 1E-06 | 1E-06 | 2E-06 | 8E-07 | 5E-07 | 2E-06 | 7E-07 | 4E-07 | No Data |
| | Beef Cattle - Direct Applied | 0.049 lb ai/animal | | 5E-06 | 3E-06 | 2E-06 | 4E-06 | 1E-06 | 1E-06 | 3E-06 | 1E-06 | 8E-07 | No Data |
| | Swine - Direct Applied | 0.0049 lb ai/animal | | 5E-07 | 3E-07 | 2E-07 | 4E-07 | 1E-07 | 1E-07 | 3E-07 | 1E-07 | 8E-08 | No Data |
| | Lactating Dairy Cattle - Direct Applied | 0.0013 lb ai/animal | | 1E-07 | 7E-08 | 6E-08 | 9E-08 | 4E-08 | 3E-08 | 9E-08 | 3E-08 | 2E-08 | No Data |
| | Poultry Buildings (Walls, Ceilings, Floors, Larvicide) - | 0.00077 lb ai/sq ft | 20,000 sq ft | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 6E-07 | No Data |
| | Poultry Buildings (Floor Management, Fowl Tick, Larvicide) | 0.00064 lb ai/sq ft | | 3E-06 | 2E-06 | 1E-06 | 2E-06 | 9E-07 | 6E-07 | 2E-06 | 9E-07 | 5E-07 | No Data |
| | Poultry (Caged) - Direct Applied | 0.00032 lb ai/bird | 20,000 birds | 2E-06 | 9E-07 | 7E-07 | 1E-06 | 5E-07 | 3E-07 | 1E-06 | 4E-07 | 3E-07 | No Data |
| | Poultry Buildings (Flies Residual) | 0.00013 lb ai/sq ft | 20,000 sq ft | 6E-07 | 4E-07 | 3E-07 | 5E-07 | 2E-07 | 1E-07 | 5E-07 | 2E-07 | 1E-07 | No Data |
| | Poultry (Chicken on Litter) - Direct Applied | 0.000078 lb ai/bird | 20,000 birds | 4E-07 | 2E-07 | 2E-07 | 3E-07 | 1E-07 | 8E-08 | 3E-07 | 1E-07 | 6E-08 | No Data |
| | Poultry Floor Management | 0.000064 lb ai/sq ft | 20,000 sq ft | 3E-07 | 2E-07 | 1E-07 | 2E-07 | 9E-08 | 6E-08 | 2E-07 | 9E-08 | 5E-08 | No Data |
| (9d) Liquid: Backrubber or Facerubber | Cattle - Direct Applied | 0.077 lb ai/gallon | 50 gallons | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | 8E-08 | 1E-08 | 1E-08 | No Data |
| | | 0.064 lb ai/gallon | | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | 7E-08 | 1E-08 | 9E-09 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| (10a) Wettable Powder: Backpack Sprayer | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 4E-06 | 4E-06 | 3E-06 | 4E-06 | 4E-06 | 2E-06 | 4E-06 | 4E-06 | 2E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | 2E-06 | 2E-06 | 1E-06 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00016 lb ai/sq ft | | 8E-07 | 8E-07 | 6E-07 | 8E-07 | 8E-07 | 5E-07 | 8E-07 | 7E-07 | 5E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.000080 lb ai/sq ft | | 4E-07 | 4E-07 | 3E-07 | 4E-07 | 4E-07 | 2E-07 | 4E-07 | 4E-07 | 2E-07 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 1E-08 | 1E-08 | 7E-09 | 9E-09 | 9E-09 | 6E-09 | 9E-09 | 9E-09 | 6E-09 | No Data |
| (10b) Wettable | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Powder: Manually-Pressurized Handwand | Swine - Direct Spray | 0.020 lb ai/animal | | 7E-05 | 5E-07 | 5E-07 | 7E-05 | 4E-07 | 3E-07 | 7E-05 | 3E-07 | 3E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 1E-04 | 1E-06 | 1E-06 | 1E-04 | 7E-07 | 6E-07 | 1E-04 | 7E-07 | 6E-07 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 7E-05 | 5E-07 | 5E-07 | 7E-05 | 4E-07 | 3E-07 | 7E-05 | 3E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 6E-05 | 4E-07 | 4E-07 | 6E-05 | 3E-07 | 3E-07 | 6E-05 | 3E-07 | 2E-07 | No Data |
| | | 0.00016 lb ai/sq ft | | 3E-05 | 2E-07 | 2E-07 | 3E-05 | 1E-07 | 1E-07 | 3E-05 | 1E-07 | 1E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 1E-05 | 1E-07 | 1E-07 | 1E-05 | 7E-08 | 6E-08 | 1E-05 | 7E-08 | 6E-08 | No Data |
| | Kennels, Yards, Campgrounds, Picnic Areas, and Recreational Parks | 0.000040 lb ai/sq ft | 1,000 sq ft (spot) | 4E-07 | 3E-09 | 3E-09 | 4E-07 | 2E-09 | 2E-09 | 4E-07 | 2E-09 | 1E-09 | No Data |
| (10d) Wettable Powder: Fogging Equipment (handheld, portable, and stationary) | Poultry (Floor Management) | 0.0016 lb ai/bird | 20,000 birds | 3E-04 | 3E-04 | 3E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | | 0.00078 lb ai/sq ft | 100,000 sq ft | 7E-04 | 7E-04 | 7E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 2E-04 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| (10e) Wettable Powder: Rotary Duster (Dust - | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | 20,000 sq ft | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| Plunger Data as Surrogate) | | | | | | | | | | | | | |
| (10f) Wettable Powder: Plunger Duster (Dust Data as Surrogate) | Poultry (Floor Management) | 0.0016 lb ai/bird | 1,000 birds | 3E-05 | 6E-06 | 6E-06 | 3E-05 | 4E-06 | 4E-06 | 2E-05 | 4E-06 | 3E-06 | No Data |
| | | 0.00078 lb ai/sq ft | 1,000 sq ft | 1E-05 | 3E-06 | 3E-06 | 1E-05 | 2E-06 | 2E-06 | 1E-05 | 2E-06 | 2E-06 | No Data |
| | Poultry (Floor Management Litter) | 0.00023 lb ai/sq ft | | 4E-06 | 9E-07 | 8E-07 | 4E-06 | 6E-07 | 5E-07 | 4E-06 | 6E-07 | 5E-07 | No Data |
| (11a) Dust: Self-Treating Dust Bag | Cattle | 0.75 lb ai/dust bag | 10 dust bags | 1E-04 | 3E-05 | 3E-05 | 1E-04 | 2E-05 | 2E-05 | 1E-04 | 2E-05 | 2E-05 | No Data |
| | | 0.38 lb ai/dust bag | | 6E-05 | 1E-05 | 1E-05 | 6E-05 | 1E-05 | 9E-06 | 6E-05 | 9E-06 | 8E-06 | No Data |
| | | 0.13 lb ai/dust bag | | 2E-05 | 5E-06 | 5E-06 | 2E-05 | 3E-06 | 3E-06 | 2E-05 | 3E-06 | 3E-06 | No Data |
| (11b) Dust: Shaker Can (Plunger Data Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 1E-03 | 8E-05 | 7E-05 | 1E-03 | 4E-05 | 3E-05 | 1E-03 | 4E-05 | 3E-05 | No Data |
| | | 0.0038 lb ai/animal | | 6E-04 | 4E-05 | 4E-05 | 6E-04 | 2E-05 | 2E-05 | 6E-04 | 2E-05 | 1E-05 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 2E-04 | 1E-05 | 1E-05 | 2E-04 | 7E-06 | 5E-06 | 2E-04 | 6E-06 | 4E-06 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/ bird | 1,000 birds | 2E-04 | 2E-05 | 1E-05 | 2E-04 | 8E-06 | 6E-06 | 2E-04 | 7E-06 | 5E-06 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 1E-04 | 8E-06 | 7E-06 | 1E-04 | 4E-06 | 3E-06 | 1E-04 | 4E-06 | 3E-06 | No Data |
| | Swine - Bedding | 0.00020 lb ai/sq ft | | 8E-05 | 5E-06 | 5E-06 | 8E-05 | 3E-06 | 2E-06 | 8E-05 | 2E-06 | 2E-06 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/ Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 4E-05 | 3E-06 | 2E-06 | 4E-05 | 1E-06 | 1E-06 | 4E-05 | 1E-06 | 8E-07 | No Data |
| (11c) Dust: Rotary Duster (Plunger Data as Surrogate) | Cattle, Swine – Direct Applied | 0.0075 lb ai/animal | 400 animals | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | | 0.0038 lb ai/animal | | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Cattle – Direct Applied | 0.0013 lb ai/animal | | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 20,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 20,000 sq ft | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 20,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| (11d) Dust: Plunger Duster | Poultry (Dust Box) – Direct Applied | 0.00060 lb ai/bird | 1,000 birds | 2E-03 | 3E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | 2E-03 | 2E-04 | 2E-04 | No Data |
| | Poultry (Floor Management) | 0.00030 lb ai/sq ft | 1,000 sq ft | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 5E-06 | 4E-06 | 3E-05 | 5E-06 | 4E-06 | No Data |
| | Poultry (Wire Cage) – Direct Applied | 0.00010 lb ai/bird | 1,000 birds | 8E-04 | 1E-04 | 1E-04 | 8E-04 | 1E-04 | 1E-04 | 8E-04 | 1E-04 | 1E-04 | No Data |
| (12a) Paint: Brush or Roller | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 3E-06 | 4E-07 | 4E-07 | 3E-06 | 4E-07 | 3E-07 | 3E-06 | 4E-07 | 3E-07 | No Data |
| | | 0.077 lb ai/gallon | | 3E-06 | 4E-07 | 4E-07 | 3E-06 | 4E-07 | 3E-07 | 3E-06 | 3E-07 | 3E-07 | No Data |
| | | 0.064 lb ai/gallon | | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | 2E-07 | 3E-08 | 3E-08 | No Data |
| | | 0.03 lb ai/gallon | | 1E-06 | 1E-07 | 1E-07 | 1E-06 | 1E-07 | 1E-07 | 1E-06 | 1E-07 | 1E-07 | No Data |

| Table L.3. TCVP Occupational Handler Cancer Risk Estimates – Contract/ Commercial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/ Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| (12b) Paint: Airless | Poultry (Roost Paint) | 0.08 lb ai/gallon | 2 gallons | 7E-07 | 3E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | No Data |
| | | 0.077 lb ai/gallon | | 7E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | 6E-07 | 2E-07 | 2E-07 | No Data |
| | | 0.064 lb ai/gallon | | 6E-08 | 2E-08 | 2E-08 | 5E-08 | 2E-08 | 1E-08 | 5E-08 | 1E-08 | 1E-08 | No Data |
| | | 0.03 lb ai/gallon | | 3E-07 | 1E-07 | 9E-08 | 2E-07 | 7E-08 | 7E-08 | 2E-07 | 7E-08 | 6E-08 | No Data |
| (13) Solid Feed Additive for Feed Through Applications via Cup (Granular Data as Surrogate) | Horse Feed | 0.0015 lb ai/animal | 500 horses | 3E-09 | 2E-09 | 2E-09 | 2E-09 | 5E-10 | 5E-10 | 2E-09 | 3E-10 | 3E-10 | No Data |
| | | 0.00077 lb ai/animal | | 2E-09 | 1E-09 | 1E-09 | 1E-09 | 3E-10 | 3E-10 | 9E-10 | 2E-10 | 2E-10 | No Data |
| | Cattle Feed | 0.0022 lb ai/animal | 1,000 cows | 5E-08 | 3E-08 | 3E-08 | 3E-08 | 8E-09 | 8E-09 | 3E-08 | 5E-09 | 5E-09 | No Data |
| | | 0.0017 lb ai/animal | | 4E-08 | 2E-08 | 2E-08 | 2E-08 | 6E-09 | 6E-09 | 2E-08 | 4E-09 | 4E-09 | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loaders** | | | | | | | | | | | | | |
| (10c) Wettable Powder: | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Scenario | Crop or Target | App. Rate[a] (lb ai/ unit) | Area Treated[b] (units/ day) | Contract/Commercial For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | SL/NoG No R | SL/G NoR | DL/G No R | SL/NoG PF5 R | SL/G PF5 R | DL/G PF5 R | SL/No G PF10 R | SL.G PF10 R | DL/G PF10 R | EC |
| Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 5E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 2E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 5E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| **Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>MRID 42622301 | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | No Data | 7E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | No Data | 3E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.00016 lb ai/sq ft | | No Data | 1E-06 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |
| | | 0.000080 lb ai/sq ft | | No Data | 7E-07 | No Data | No Data | No Data | No Data | No Data | No Data | No Data | No Data |

| Table L.4. TCVP Occupational Handler Cancer Risk Estimates for Exposure Scenario 10c with Use of Chemical-Specific Data and PHED – Contract/Commercial | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Scenario** | **Crop or Target** | **App. Rate[a] (lb ai/ unit)** | **Area Treated[b] (units/ day)** | **Contract/Commercial** For risk management purposes, the currently labeled level of PPE and EC has been identified (shaded) for each individual exposure scenario. | | | | | | | | | |
| | | | | **SL/NoG No R** | **SL/G NoR** | **DL/G No R** | **SL/NoG PF5 R** | **SL/G PF5 R** | **DL/G PF5 R** | **SL/No G PF10 R** | **SL.G PF10 R** | **DL/G PF10 R** | **EC** |
| **Mixer/Loader/Applicators** | | | | | | | | | | | | | |
| (10c) Wettable Powder: Mechanically -Pressurized Handgun<br><br>PHED | Beef Cattle - Direct Spray | 0.040 lb ai/animal | 400 animals | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 7E-07 | No Data |
| | Swine - Direct Spray | 0.020 lb ai/animal | | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Poultry (Floor Management Litter, Fowl Tick), Poultry Droppings, Manure Piles, Garbage Piles, Under Feed Troughs | 0.00080 lb ai/sq ft | 20,000 sq ft | 2E-05 | 1E-05 | 9E-06 | 1E-05 | 6E-06 | 4E-06 | 1E-05 | 5E-06 | 3E-06 | No Data |
| | Poultry (Wire Cages) - Direct Spray | 0.00040 lb ai/bird | 20,000 birds | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |
| | Dairy Barns, Poultry Houses, Swine Barns, or other Animal Buildings | 0.00032 lb ai/sq ft | 20,000 sq ft | 8E-06 | 4E-06 | 4E-06 | 6E-06 | 2E-06 | 2E-06 | 6E-06 | 2E-06 | 1E-06 | No Data |
| | | 0.00016 lb ai/sq ft | | 4E-06 | 2E-06 | 2E-06 | 3E-06 | 1E-06 | 8E-07 | 3E-06 | 1E-06 | 7E-07 | No Data |
| | | 0.000080 lb ai/sq ft | | 2E-06 | 1E-06 | 9E-07 | 1E-06 | 6E-07 | 4E-07 | 1E-06 | 5E-07 | 3E-07 | No Data |

Message

**From**: Parker, James [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F2D8B49CA67A44218A01D83521029F67-JAMES PARKER]
**Sent**: 2/14/2017 9:31:35 PM
**To**: Nguyen, Khue [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53463f4f956d4772a6ada2f68debfcb8-Nguyen, Khue]
**Subject**: Tetrachlorvinphos: Case summary and DCI Tracker
**Attachments**: Tetrachlorvinophos.doc; DCI Status Report.current .doc

Khue,

I attached a two documents above which I used to track the daily work associated with TCVP and the beans associated with my DCIs.

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