US Environmental Protection Agency
Office of Pesticide Programs

Final Guidance for Waiving Sub-Acute Avian Dietary Tests for Pesticide Registration and Supporting Retrospective Analysis

February 2020

ED_005325D_00000935-00001

1. Introduction

This document describes the results and implications of a retrospective study that the United States Environmental Protection Agency (EPA) and stakeholders conducted to inform its consideration of reduced animal testing in the form of waiver requests for sub-Acute Avian Dietary Tests when registering conventional pesticides that would be used outdoors. The document also provides additional points to consider when evaluating a waiver request based available physical/chemical, mechanism of action, and other toxicological information for a pesticide. This document is applicable to waiver requests for avian sub-acute lethal dietary studies for waterfowl and upland gamebird species (Guideline 850.2200) as required under 40 *CFR* section 158.630 and does not apply to consideration of waivers for avian sub-acute dietary studies for passerine species in lieu of a passerine acute single oral dose study (guideline 850.2100 as required under 40 *CFR* section 158.630).

EPA registers pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under 40 *CFR* part 158, EPA requires supporting studies to meet FIFRA safety standards. There is flexibility, however, in implementing Part 158. Additional data can be required (§§158.30, 158.75), alternative approaches can be accepted (§§158.30, 158.70), and studies can be waived (§§158.30, 158.45). The 2007 National Academy of Sciences (NAS) report on Toxicity Testing in the 21st Century[1] describes a new vision for toxicity testing. EPA's Office of Pesticide Programs (OPP) has developed a Strategic Direction for New Pesticide Testing and Assessment Approaches[2] which describes the EPA approach to implementing the NAS vision. One component of this is improved approaches to traditional toxicity tests to minimize the number of animals used while expanding the amount of information obtained. OPP's document on *Guiding Principles for Data Requirements*[3] emphasizes only requiring data that inform regulatory decision making and avoiding unnecessary use of time and resources, data generation costs, and animal testing. Waiving studies, when they offer little additional scientific information or public health protection, is an important component of the guiding principles for data requirements. This allows OPP staff to focus on the information most relevant to an assessment and still ensure there is sufficient information for regulatory decisions that are protective of public health and the environment.

For the registration of conventional pesticides used outdoors, OPP typically requires two avian acute oral toxicity studies (one with an upland game or waterfowl species and one with a passerine species) and two avian sub-acute dietary studies (one with an upland game species and one with a waterfowl species). OPP's Pesticide Assessment Guidelines Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms[4] presents the rationale for both the acute oral and

---

[1] National Research Council. 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington DC: The National Academies Press. https://www.nap.edu/read/11970/chapter/2.

[2] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science

[3] https://www.epa.gov/pesticide-registration/guiding-principles-data-requirements

[4] Pesticide Assessment Guidelines Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms https://nepis.epa.gov/Exe/ZyNET.exe/P1007WF5.TXT?ZyActionD=ZyDocument&Client=EPA&Index=1981+Thru+1985&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5Czyfiles%5CIndex%20Da

ED_005325D_00000935-00002

the sub-acute dietary tests. Among the rationale for requiring both tests was a stated concern that reliance on a single test may be "misleading in evaluating a pesticide that exhibits cumulative effects or one that is easily degraded" (note these characteristics are considered in this guidance when making a decision on the need for a sub-acute dietary toxicity test). Furthermore, Subdivision E maintains that the sub-acute dietary test is insufficient for characterizing the risks of granular pesticide formulations. Finally, Subdivision E asserts that the single oral dose study should be retained for hazard classification purposes. The Ecological Committee of FIFRA Risk Assessment Methods, ECOFRAM 1999[5] provided further discussion of the relative strengths and limitations for the studies. This discussion was from the perspective of incorporation of the effects endpoint information into risk assessments that include refined methods beyond screening work. ECOFRAM summarized several aspects of the avian dietary test that limits its utility in refined assessments:

- The study cannot provide a dose estimate for the effects endpoint because test organism consumption estimates are confounded by spillage, the lack of daily estimates of consumption, and mortalities occurring before study termination.
- The five-day exposure window is arbitrary, having more to do with laboratory expedience than any avian behavioral or toxicological factor.
- Toxicity is further confounded by the willingness of birds to consume food and the methodology cannot account for such behaviors as enhanced feeding rate during migration and the effect of assimilative energy differences between laboratory and field dietary matrices.
- Dietary concentrations are held constant during the study, limiting the use of food item degradation estimates in risk assessment.

Pesticide risk assessments evaluate potential risks to non-target bird species by calculating risk quotients (RQs) using the most sensitive endpoint from each type of study (i.e., acute oral and sub-acute dietary), the highest of which usually drives the risk conclusions and ultimately the risk management decisions. Anecdotally, OPP risk assessors and risk managers have generally found that the endpoints from acute oral studies normally give higher RQs than RQs from the sub-acute dietary studies, suggesting that the acute oral RQ calculation usually represents a protective approach. To explore this anecdotal position, a joint effort with People for the Ethical Treatment of Animals (PETA) was undertaken to explore the quantitative and qualitative contributions of risk assessment methods using the single oral dose and the sub-acute dietary toxicity endpoints to the overall conclusions of acute avian risk.

EPA in collaboration with PETA retrospectively compared the conclusions of a series of publicly available pesticide risk assessments, reached using the single oral dose and the dietary test

---

ta%5C81thru85%5CTxt%5C00000017%5CP1007WF5.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=hpfr&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=1&SeekPage=x&ZyPURLL

[5]ECOFRAM Terrestrial Draft Report (ECOFRAM 1999) https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/ecofram-terrestrial-draft-report

endpoints (Hilton et al. 2019[6]). This analysis focused on conventional pesticides that were submitted to the Agency for registration between 1998 and 2017. The OPP/PETA analysis, discussed in **Section 2** below, addressed the question of whether OPP can confidently assess acute risk for birds using the single oral dose protocol alone. This was done by considering how often sub-acute dietary-based RQs have quantitatively and/or qualitatively driven risk assessment conclusions. OPP used the results of this analysis to support a draft policy statement in **Section 4** to accept waiver requests for avian sub-acute dietary studies that meet certain criteria. We expect that most, but not all, conventional pesticides would meet these criteria.

2. Retrospective Analysis

2.1. A summary of the retrospective analysis conducted by OPP and PETA is provided below.

2.1.1. Dataset for Analysis

The analysis focused on pesticides registered through OPP's Registration Division (RD) from 1998 through 2017. The rationale for selecting this date period was to provide a sampling of the most recent chemical classes reasoning that these classes are the least mature in terms of addition of new compounds within the class so likely represent classes for which new chemicals will be encountered and which decisions of avian testing will be required. The chemical set was comprised of 52 insecticides, 62 fungicides, 46 herbicides, and 22 compounds of other pesticidal target (*e.g.* rodenticide). For the complete list of the chemicals considered, see **Attachment A**. Attachment A also presents a list of the mechanism of action represented by the chemical set.

2.1.2. Selection of Documents and Data

EPA's Pesticide Chemical Search (ChemSearch) online database[7] was searched for publicly available documents inclusive of the 181 chemicals mentioned above. Information extraction centered on documents logically assumed to contain reported effects endpoints for the avian acute oral and sub-acute dietary tests. These documents included ecological risk assessments (ERA), problem formulations (PF), preliminary risk assessments (PRA), and final work plans (FWP). The available documents in these categories were downloaded and reviewed for relevant toxicity and physicochemical information. The ERA and PRA documents typically contained toxicity information for both acute and sub-acute endpoint values, as well as RQ values. If the PF and FWP documents contained LD_{50} and LC_{50} values, but not RQ values, then additional information from data evaluation records (DER), EPA reviews of studies submitted by registrants, were examined for chemicals that were reported as a definitive test to ensure all relevant information was collected for analysis. If the PF and FWP documents reported chemical toxicity by limit test (*i.e.* one single high dose or concentration tested), and no additional studies were requested for the chemical, then no quantitative estimate of acute avian risk was presumed.

---

[6] Hilton, G.M. E. Odenkirchen, M. Panger, G. Waleko. A. Lowit, A.J. Clippinger. 2019. Evaluation of the avian acute oral and sub-acute dietary toxicity test for pesticide registration. Regulatory Toxicology and Pharmacology, 105:30-35

[7] USEPA ChemSearch https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1

2.2. Overview of Dataset

Of the 181 pesticides searched on the ChemSearch website, 119 chemicals had available risk assessment documents that could be used for the acute oral and sub-acute dietary RQ comparative analysis. The remaining 62 pesticides were not included in comparative acute versus sub-acute RQ analysis because documents containing information on acute oral and sub-acute dietary studies were not available via ChemSearch. Additional evaluation was done on these 62 excluded chemicals to determine if they represented unique or underrepresented modes of action as described below.

For 87 of the 119 chemicals, both the oral and dietary reported effects endpoints were from limit tests. Limit testing involves a study where the LD50 or the LC50 for the active ingredient was reported as being greater than a single upper limit exposure level (5000mg/kg-bw for LD50 acute oral and 2000 mg/kg-diet for dietary) or for a dose/exposure levels that is at or greater than estimated environmental concentrations under labeled use). For 10 chemicals, the endpoints were from a definitive test for both oral and dietary tests. Definitive tests are conducted over multiple dose or exposure levels and return a defined LD50 or LC50. The endpoints for 17 chemicals were from a limit test for the sub-acute dietary study and from a definitive test for the acute oral study. In 5 cases, the acute oral endpoint was from a limit test while the sub-acute dietary endpoint was from a definitive test.

It is important to note that some chemical risk assessment documents reported definitive toxicity test results but did not have reported RQ values. To ensure that the tests were reported accurately in the downloaded risk assessment documents (*e.g.*, an acute oral test with an LD_{50} reported as 2000 mg a.i./kg-bw instead of >2000 mg a.i./kg-bw) these sub-acute dietary and acute oral toxicity studies were retrieved from problem formulation documents and study DERs to eliminate spurious results from erroneous endpoint reporting in the available risk assessment documents.

For 6 pesticides, the risk assessment documents failed to report toxicity information pertinent to the avian effects characterization. In these cases, EPA reviewed DERs and earlier risk assessments to determine the avian study outcome. These chemicals were found to have a new use registration that did not require the acute avian test submission (*e.g.*, indoor uses or were found to have been conducted as a limit test), and therefore no acute avian risk is presumed.

2.3. Comparison of Risk Quotients from Avian Acute Oral and Sub-Acute Dietary Studies

In 99% of cases (118 of 119 chemicals evaluated quantitatively) the RQ values for the sub-acute dietary risk assessment approach were lower than the RQs calculated using the single oral dose acute effects endpoint. Consequently, in 99% of cases evaluated, the conclusions of the risk assessments were driven by the results of RQ calculations using the single oral dose data.

It is notable that the single exception for the comparisons was for a second-generation anticoagulant rodenticide. This is a class of compounds for which repeat exposures can lead to accumulation of the pesticide in target organs, and the clotting factor synthesis mode of action would suggest that exposure persisting over time would also have cumulative effects concerns

(continued inhibition of clotting factor synthesis results in depletion of existing clotting factor pool over time).

2.4. Modes of Action and Analogue Considerations

Not all chemical risk assessment cases considered allowed for a quantifiable comparison of RQs using the effects data from the sub-acute and acute studies. Of the 181 chemicals searched in the ChemSearch website, 62 were not included in the above analysis because public documents containing information on acute oral and sub-acute dietary studies were not available through the ChemSearch database.

A review of the chemical modes of action (MOA) was conducted for all the chemicals to determine whether the MOAs for the 62 chemicals lacking public documents were covered by one of the pesticides for which the comparison of RQs was completed (*i.e.,* did they share a chemical class with one of the chemicals included in the analysis?). Seven of the 62 chemicals in six pesticide mode of action classes did not share a chemical class with a pesticide included in the quantitative RQ comparison. The unrepresented pesticide mode of action codes, chemical classes, and target sites are as follows:

IRAC/HRAC/FRAC putative mechanism of action code	Chemical Class	Target site	Chemical Name
insecticide 2B	Phenylpyrazole	GABA-gated chloride channel blocker	ethiprole
insecticide 24A	Phosphide	Mitochondrial complex IV electron transport inhibitor	phosphine gas
Insecticide Unassigned	Propenyl oxy ether	Insect cell growth inhibitor	pyridalyl
FungicideA1	Acylalanine	RNA polymerase	benalaxyl-M
Fungicide B2	N-phenyl carbamates	ß-tubulin assembly in mitosis	diethofencarb
Fungicide M	Sulfamides/quinone	multi-site contact activity	dithianon, tolylfluanid

Of these cases above, one (phosphine gas), because of its gaseous state would not be amenable to a dietary residue-based risk assessment and so would not rely on subacute dietary toxicity endpoints for the risk assessment. One, pyridalyl, represents a potentially bioaccumulative compound which would trigger an exception to the waiver process as outlined later in this document. The remaining compounds have not undergone ecological risk assessments to support regulatory decision-making primarily because the regulatory decisions were import tolerances.

Therefore, in most of the unevaluated cases (87%), the chemical class was represented by an analogue in the RQ analysis, and the remaining cases are either immaterial to the analysis because of a lack of dietary exposure pathway, the lack of any regulatory decisions requiring an ecological risk assessment or are material to pesticide characteristics that would form criteria for an exception to the waiver policy. Therefore, the available analyses lend confidence in the results of the quantitative evaluation of RQs conducted to inform the expectations for risk assessments going forward.

3. Discussion: Implications of the Retrospective Analysis on the Utility of Avian Sub-Acute Dietary Studies in Select Situations

This analysis is intended to address whether OPP can confidently assess acute risk for birds using a reduced suite of effects studies focusing on the single oral dose protocol. As described above, the retrospective analysis indicates that for almost all the pesticides in which the risk conclusions across study types could be compared (>99%), the sub-acute dietary results had an obvious lack of impact on the risk conclusions already reached using the acute oral data. The one exception involved a chemical that impacts birds via accumulative damage and results in delayed mortality (*i.e.*, an anti-coagulant pesticide). For this chemical, the risk quotients using the sub-acute dietary study risk quotients results were larger than those reached using the acute oral study data. While in this particular case the conclusions of the risk assessment were not impacted relative to exceedance of OPP levels of concern thresholds, in other cases such a larger risk quotient observed for the dietary-based analysis might alter risk management decisions. Encountering this nuanced exception in the analysis has led to include in section 4 of this document a consideration of pesticide accumulation and toxicity properties that could likely trigger a denial of a waiver.

Furthermore, a majority of pesticides that could not be evaluated because of a lack of avian risk assessment information shared a MOA with a chemical included in the analysis (*i.e.*, they had analogs that were included in the analysis). There is a small subset of chemicals that had unique MOAs and did not share an analog with chemicals included in the analysis. Therefore, there is uncertainty in how the risks based on avian acute oral and sub-acute dietary studies may compare for this small subset of MOAs chemicals and any chemical not sharing a MOA with a chemical included in the analysis. EPA has included mechanism of action considerations in section 4 of this document as an information area for consideration regarding a request to waive avian sub-acute dietary testing.

A strength of existing sub-acute dietary toxicity tests is that the study can account for situations where the properties of the chemical are such that there may be a rate-limiting step in the absorption of the compound. The more protracted nature of the exposure period (the subject animals receive a dose spread out across several days of dietary consumption) has the potential to not reach absorption limits of the chemical as opposed to the intensive single oral exposure study. In such cases of rate limited absorption, there is the potential for the single oral dose study to underestimate effects under field conditions. Also, in cases where effects may be cumulative over time or the chemical may accumulate in the body or selected sites of action over time (e.g., the liver for second-generation anticoagulant rodenticides) to a point where a biological effects threshold is reached, the sub-acute dietary study may provide a more relevant short-term effects measure than the single oral dose study. The subsequent waiver recommendation below includes points to consider from available data in this regard.

4. Draft Waiver Guidance

OPP believes this retrospective analysis demonstrates that waivers may be granted for avian sub-acute dietary testing unless one of the conditions described below is triggered. Possible exceptions to the waiver could include:

- Chemicals with unique/unspecified MOAs or those chemicals with MOAs not evaluated in the retrospective analysis unless the waiver request presents evidence that the chemical's MOA is not reasonably expected to result in accumulative damage. To the extent that EPA receives studies on additional MOAs that demonstrate such a showing, EPA would likely waive the avian sub-acute dietary testing for pesticide with these additional MOAs without requiring additional information.
- Chemicals with MOAs that suggest a mechanism for accumulative damage (i.e., where pesticidal effects increase with repeated exposure over time)
- Chemicals with a high potential for bioaccumulation or a saturable facilitated mechanism of adsorption, as indicated by a weight of evidence evaluation of the following properties:
    - High octanol-water partition coefficient ($\log K_{ow} \geq 4$) and high molecular weight
    - High bioconcentration factor in fish (BCF>1000) (OCPPT850.1730[8]) or information suggesting limited metabolism and excretion
        - Bioconcentration study showing low pesticide clearance rates following cessation of exposure
    - Mammalian toxicity and animal residue studies
        - Results from a metabolism study (OPPTS 870.7485[9]) that shows pesticide absorption rates significantly lower at high doses than low doses or clearance rates that are slow enough to suggest that repeated doses with result in accumulated body burden
        - The use of daily oral dose exposure in subchronic and chronic mammalian studies when the usual exposure route is dietary
        - Any data showing acute dietary endpoints that are lower than acute oral endpoints in mammalian testing when adjusted for daily ingested dose.
        - Results for residue studies (OPPTS 860.1480[10]) showing:
            - pesticide absorption rates significantly lower at high doses than low doses suggestive of a saturable absorption mechanism and/or
            - very low rates of metabolism and excretion (*e.g.* little to know proportion of the parent found as metabolites, excretion rats on the order of weeks)
- Chemicals in which an avian acute oral study cannot be conducted (*e.g.*, when the chemical causes regurgitation via the acute oral route)

---

[8] USEPA 2016. Ecological Effects Test Guidelines. OCSPP 850.1730 Fish Bioconcentration Factor. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0154-0031

[9] USEPA 1998. Health Effects Test Guideline OCSPP 870.7485 Metabolism and Pharmacokinetics https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0156-0047

[10] USEPA 1996. Residue Chemical Test Guidelines. 860.1480 Meat/Milk/Poultry/Eggs https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0155-0012

ED_005325D_00000935-00008

Applicants should submit requests to waive the data requirement for avian sub-acute dietary toxicity studies as part of their registration application through existing processes. Waiver requests should include all relevant information to support an EPA evaluation of the evidentiary grounds for the waiver request to include the rationale for why the proposed chemical is not subject to the criteria for waiver denial under Section 4 of this document.

This document and its finding do not necessarily preclude sub-acute dietary testing for birds. Despite the protection nature of risk assessments relying on the single oral dose acute endpoint, avian sub-acute dietary testing may bring perspective to a risk assessment and improve the knowledge base supporting a regulatory decision. For example, avian sub-acute dietary studies are a logical default study to arrive at a passerine lethal acute toxicity endpoint in cases where test subject regurgitation has been demonstrated to be an insurmountable obstacle to establishing a reliable single oral dose lethal endpoint. Similarly, the ability for the dietary study to account for the potential for dietary matrix to be mitigatory for chemical absorption and thus toxicity may also be a situation where additional information may be useful. The repeated and expected lower episodic doses associated with the dietary study, if showing diminished effects relative to a single oral challenge dose, may provide evidence of compensatory mechanisms in the test organism nature of the subacute. Finally, inclusion of subacute dietary studies has the potential to increase the number of testing avian species, theoretically affecting a distributional consideration in the avian risk assessment, but only if the studies were rigorous enough to allow for dose-based endpoints to be established.

5. Effect on Animal Testing Burden

Granting sub-acute dietary toxicity test waivers under the conditions described above has the potential to reduce the number of animals tested by a total of 60 birds per test (*i.e.,* 10 birds in control and 10 birds in each of five tested dietary concentrations), based on the recommendation outlined in OCSPP 850.2100. There are typically two species tested, bringing the reduction in the number of birds up to 120 per chemical. With a typical average of 6 new chemicals registered per year, the adoption of this guidance can reduce the number of animals tested by approximately 720 animals per year. In cases where the avian dietary study is waived, fewer species will be tested (i.e., two rather than three) thereby increasing uncertainty regarding species sensitivity.

Appendix A
Lists of Pesticide Active Ingredients for the Retrospective Analysis and the Mechanisms of Pesticidal Action

A

INSECTICIDE

Acequinocyl
Acequinocyl

Acetamiprid
Acetamiprid

Avermectins
Emamectin Benzoate
Milbemectin

Benzoylureas
Novaluron
Noviflumuron
Flufenoxuron
Lufenuron
Teflubenzuron

Beta-ketonitrilederivatives
Cyflumetofen

Bifenazate
Bifenazate

Buprofezin
Buprofezin

Butenolides
Flupyradifurone

Cypermethrin
alpha-Cypermethrin

Diacylhydrazines
Methoxyfenozide

Diamides
Chlorantraniliprole
Cyantraniliprole
Flubendiamide

Etoxazole
Etoxazole

Flonicamid
Flonicamid

METI acaricides and insecticides
Fenazaquin
Tolfenpyrad
Fenpyroximate
Tebufenpyrad

Neonicotinoids
Thiamethoxam
Clothianidin
Dinotefuran
Thiacloprid

Oxadiazines
Indoxacarb

Phenylpyrazoles
Ethiprole

Phosphides
Phosphine Gas

Pyrethroids/Pyrethrins
Etofenprox
Imiprothrin
Flumethrin

Pyridalyl
Pyridalyl

Pyridine azomethine
Pymetrozine
Pyrifluquinazon

Semicarbazones
Metaflumizone

Spinosyns
Spinetoram

Sulfoximines
Sulfoxaflor

Tetronic and Tetramic
Spirotetramat
Spirodiclofen
Spiromesifen

NA
Metofluthrin
Momfluorothrin
Lithium (perfluorooctane)-Sulfonate

B

HERBICIDE

Alkylazines
Indaziflam

Aryloxyphenoxy-propionate 'FOPs'
Clodinafop-propargyl
Cyhalofop-butyl

Arylpicolinate
Halauxifen-methyl

Cyclohexanedione 'DIMs'
Tralkoxydim

Isoxazole
Isoxaflutole

Long Chain Fatty Acid Inhibitor
Pyroxasulfone

N-phenylphthalimide
Flumioxazin

Other (PPO)
Flufenpyr-ethyl

Oxyacetamide
Flufenacet

Phenylpyrazole
Pyraflufen-ethyl

Phenylpyrazoline
Pinoxaden

Phthalamate Semicarbazone
Diflufenzopyr

Pyridine carboxylic acid
Aminopyralid
Fluroxypyr

Pyrimidinediones
Saflufenacil
Butafenacil

Pyrimidinyl(thio) benzoate
Bispyribac Sodium

Sulfonylamino carbonyl-triazolinone
Flucarbazone-sodium
Thiencarbazone-methyl
Propoxycarbazone-Sodium

Sulfonylurea
Flazasulfuron
Foramsulfuron
Imazosulfuron
Mesosulfuron-methyl
Orthosulfamuron
Sulfosulfuron
Trifloxysulfuron-sodium
Ethametsulfuron Methyl

Thiadiazole
Fluthiacet-methyl

Triazine
Propazine

Triazolinone
Amicarbazone
Carfentrazone-ethyl
Azafenidin

Triazolopyrimidine
Cloransulam-methyl
Florasulam
Penoxsulam
Pyroxsulam
Diclosulam

Triketone
Mesotrione

NA
Aminocyclopyrachlor
Bicyclopyrone
Iodosulfuronmethyl Sodium
Pyrasulfatole
Tembotrione
Topramezone

C	FUNGICIDE		D	OTHER
2,6-dinitro-anilines *Fluazinam*	**Methoxy-carbamates** Pyraclostrobin	**Toluamides** Zoxamide		Prohexadione Calcium Oxalic acid Nicarbazin Iodomethane n-methylneodecanamide Mammalian Gonadotropin Releasing Hormone Ammonium Nitrate Calcium Nitrate Cuprous Chloride EH-2001 Oxysilver Nitrate Potassium tri-iodide S-Dimethenamid Sodium nitrite Tepraloxydim Zona-Stat *Fluensulfone* *Fosthiazate* *Furfural* Demiditraz Forchlorfenuron PT807 (Ecolyst)-HCl VCD and Triptolide *Difenacoum* alpha-Chlorohydrin Acetaminophen Dimethyl disulfide
Acylalanines Benalaxyl-M	**Morpholines** Fenpropimorph	**Triazoles** *Flutriafol* Ipconazole *Metconazole* Bromuconazole Epoxiconazole Tetraconazole Triticonazole		
Amino-pyrazolinone *Fenpyrazamine*	**N-methoxy-pyrazole-carboxamides** Pydiflumetofen	**Triazolinthiones** *Prothioconazole*		
Anilino-pyrimidines *Cyprodinil* Mepanipyrim Pyrimethanil	**N-phenylcarbamates** Diethofencarb	**Triazolo-pyrimidylamine** Ametoctradin		
Aromatic hydrocarbons *Tolclofos-methyl*	**Oxazolidine-diones** Famoxadone	**Valinamide carbamates** Benthiavalicarb-isopropyl Iprovalicarb		
Aryloxyquinoline Quinoxyfen	**Oximino-acetates** Kresoxim-methyl Trifloxystrobin	**NA** Macleaya extract chloride		
Benzophenone Metrafenone	**Phenylacetamide** Cyflufenamid			
Benzothiadiazole Acibenzolar-s-methyl	**Phenyl-oxo-ethylthiophene amide** Isofetamid			
Benzoylpyridine Pyriofenone	**Picolinamides** Amisulbrom			
Cinnamic acid amides Dimethomorph	**Piperidines** Fenpropidin Spiroxamine			
Cyanoacetamideoxime *Cymoxanil*	**Piperidinyl-thiazoleisoxazolines** *Oxathiapiprolin*			
Cyano-imidazole Cyazofamid	**Pyrazole-4-carboxamides** *Benzovindiflupyr* *Fluxapyroxad* Penflufen Penthiopyrad Sedaxane Isopyrazam			
Dihydro-dioxazines *Fluoxastrobin*				
Dinitrophenyl-crotonates Meptyldinocap				
Ethylamino-thiazolecarboxamide Ethaboxam				
Hexopyranosylantibiotic Kasugamycin	**Pyridine carboxamides** Nicobifen			
Hydroxyanilides Fenhexamid	**Pyridinyl-ethylbenzamides** Fluopyram			
Imidazolinones Fenamidone	**Pyridinylmethyl benzamides** Fluopicolide			
Mandelic acid amides Mandipropamid	**Quinazolinone** Proquinazid			
Methoxy-acetamide Mandestrobin	**Quinones** Dithianon			
Methoxy-acrylates *Picoxystrobin*	**Sulfamides** Tolylfluanid			

ED_005325D_00000935-00012

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
INSECTICIDES	1B	Organophosphates	Acetylcholinesterase (AChE) inhibitors. Nerve action	1	0	1
	2B	Phenylpyrazoles	GABA-gated chloride channel blockers. Nerve action	0	1	1
	3A	Cypermethrin; Pyrethroids; Pyrethrins	Sodium channel modulators. Nerve action	3	1	4
	4A	Neonicotinoids	Nicotinic acetylcholine receptor (nAChR) competitive modulators. Nerve action	5	0	5
	4C	Sulfoximines	Nicotinic acetylcholine receptor (nAChR) competitive modulators. Nerve action	1	0	1

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	4D	Butenolides	Nicotinic acetylcholine receptor (nAChR) competitive modulators. Nerve action	1	0	1
	5	Spinosyns	Nicotinic acetylcholine receptor (nAChR) allosteric modulators. Nerve action	1	0	1
	6	Avermectins; Milbemycins	Glutamate-gated chloride channel (GluCl) allosteric modulators. Nerve and muscle action	1	1	2
	9B	Pyridine azomethine derivatives	Chordotonal organ TRPV channel modulators. Nerve action	2	0	2

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	10B	Etoxazole	Mite growth inhibitors. Growth regulation	1	0	1
	15	Benzoylureas	Inhibitors of chitin biosynthesis, type 0. Growth regulation	2	3	5
	16	Buprofezin	Inhibitors of chitin biosynthesis, type 1. Growth regulation	1	0	1
	18	Diacylhydrazines	Ecdysone receptor agonists. Growth regulation	1	0	1
	20B	Acequinocyl	Mitochondrial complex III electron transport inhibitors. Energy metabolism	1	0	1

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	20D	Bifenazate	Mitochondrial complex III electron transport inhibitors. Energy metabolism	1	0	1
	21A	METI acaricides and insecticides	Mitochondrial complex I electron transport inhibitors. Energy metabolism	3	1	4
	22A	Oxadiazines	Voltage-dependent sodium channel blockers. Nerve action	1	0	1
	22B	Semicarbazones	Voltage-dependent sodium channel blockers. Nerve action	1	0	1

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	23	Tetronic and Tetramic acid derivatives	Inhibitors of acetyl CoA carboxylase Lipid synthesis. Growth regulation	1	2	3
	24A	Phosphides	Mitochondrial complex IV electron transport inhibitors. Energy metabolism	0	1	1
	25A	Beta-ketonitrile derivatives	Mitochondrial complex II electron transport inhibitors. Energy metabolism	1	0	1
	28	Diamides	Ryanodine receptor modulators. Nerve and muscle action	3	0	3

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	29	Flonicamid	Chordotonal organ Modulators - undefined target site. Nerve action	1	0	1
	UN	Unknown	Unknown, pyridalyl	0	1	1
	NA	NA	NA	7	NA	7
FUNGICIDES	A1	Acylalanines	RNA polymerase I	0	1	1
	B2	N-phenyl carbamates	ß-tubulin assembly in mitosis	0	1	1
	B3	ethylamino-thiazolecarboxamide;toluamides	ß-tubulin assembly in mitosis	2	0	2
	B5	pyridinylmethyl benzamides	delocalisation of spectrin-like proteins	1	0	1

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	B6	benzoylpyridine; benzophenone	actin/myosin/fi mbrin function	1	1	2
	C2	pyrazole-4-carboxamides; N-methoxy-(phenylethyl)-pyrazolecarboxam ides; pyridinyl-ethylbenzamides; phenyl-oxo-ethyl thiophene amide; pyridine carboxamides	Complex II: succinate-dehydrogenase	8	2	10
	C3	oxazolidine-diones; Imidazolinones; oximino-acetates; methoxy-acetamide; methoxy-acrylates; methoxy-carbamates; oximino-acetates; dihydro-dioxazines	Complex III: cytochrome bc1 (ubiquinol oxidase) at Qo site (cyt b gene).	6	2	8

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	C4	picolinamides; cyano-imidazole	Complex III: cytochrome bc1 (ubiquinone reductase) at Qi site	1	1	2
	C5	dinitrophenyl-crotonates; 2,6-dinitro-anilines	uncouplers of oxidative phosphorylation	1	1	2
	C8	triazolo-pyrimidylamine	Complex III: cytochrome bc1 (ubiquinone reductase) at Qo site, stigmatellin binding sub-site	1	0	1
	D1	anilino-pyrimidines	methionine biosynthesis (proposed) (cgs gene)	1	2	3
	D3	hexopyranosyl antibiotic	protein synthesis (ribosome, initiation step)	1	0	1
	E1	quinazolinone; aryloxyquinoline	signal transduction (mechanism unknown)	1	1	2

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	F3	aromatic hydrocarbons	cell peroxidation (proposed)	1	0	1
	F9	piperidinyl-thiazoleisoxazolines	lipid homeostasis and transfer/storage	1	0	1
	G1	triazoles; triazolinthiones	C14-demethylase in sterol biosynthesis (erg11/cyp51)	4	4	8
	G2	piperidines; morpholines	Δ14-reductase and Δ8, Δ7-isomerase in sterol biosynthesis (erg24, erg2)	1	2	3
	G3	hydroxyanilides; amino-pyrazolinone	3-keto reductase, C4-de-methylation (erg27)	2	0	2
	H5	valinamide carbamates; cinnamic acid amides; mandelic acid amides	cellulose synthase	2	2	4

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	M	sulfamides; quinones	multi-site contact activity	0	2	2
	P1	benzothiadiazole (BTH)	salicylate-related	1	0	1
	U	phenylacetamide; cyanoacetamideoxime	unknown	2	0	2
	NA	NA	NA	2	0	2
HERBICIDES	A	Aryloxyphenoxy-propionate 'FOPs'	Lipid synthesis Inhiition (inhibition of ACCase)	1	0	1
	A	Cyclohexanedione 'DIMs'	Lipid synthesis Inhiition (inhibition of ACCase)	1	0	1
	A	Phenylpyrazoline 'DEN'	Lipid synthesis Inhiition (inhibition of ACCase)	1	1	2
	B	Pyrimidinyl (thio) benzoate	Inhibition of ALS (branched chain amino acid synthesis)	1	0	1

ED_005325D_00000935-00022

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	B	Triazolopyrimidine	Inhibition of ALS (branched chain amino acid synthesis)	3	1	4
	B	Sulfonylurea	Inhibition of ALS (branched chain amino acid synthesis)	7	1	8
	B	Sulfonylamino-carbonyl-triazolinone	Inhibition of ALS (branched chain amino acid synthesis)	2	1	3
	C1	Triazolinone	Inhibition of photosynthesis at photosystem II	1	0	1
	C1	Triazine	Inhibition of photosynthesis at photosystem II	1	0	1
	E	Triazolinone	Inhibition of protoporphyrinogen oxidase	1	1	2
	E	Other (PPO)	Inhibition of protoporphyrinogen oxidase	1	0	1

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	E	N-phenylphthalimide	Inhibition of protoporphyrinogen oxidase	1	0	1
	E	Thiadiazole	Inhibition of protoporphyrinogen oxidase	1	0	1
	E	Phenylpyrazole	Inhibition of protoporphyrinogen oxidase	1	0	1
	E	Pyrimidindione	Inhibition of protoporphyrinogen oxidase	1	1	2
	F	NA	Inhibition of pigment synthesis (bleaching)	1	0	1
	F2	NA	Inhibition of 4-HPPD	3	0	3
	F2	Isoxazole	Inhibition of 4-HPPD	1	0	1
	F2	Triketone	Inhibition of 4-HPPD	1	0	1

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	K3	Oxyacetamide	Inhibition of cell division (inhibition of VLCFAs)	1	0	1
	K3	Other	Inhibition of cell division (inhibition of VLCFAs)	1	0	1
	L	Alkylazines	Inhibition of cellulose synthesis	1	0	1
	O	Pyridine carboxylic acid	Synthetic Auxins	1	1	2
	O	Arylpicolinate	NA	1	0	1
	P	Phthalamate Semicarbazone	Inhibition of auxin transport	1	0	1
	NA	NA	NA	3	0	3

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
OTHER (NO DATA)	Oxalic acid	Antimicrobial Pesticide				
	Nicarbazin	Egg Hatch Reduction in Resident Canada Geese				
	Macalayea Extract, Macleaya extract chloride	Fungicide				
	n-methylneodecanamide	Insect Repellent				
	Lithium (perfluorooctane) Sulfonate	Insecticide				
	Mammalian Gonadotropin Releasing Hormone	Mammalian Contraceptive				
	Ammonium Nitrate	NA				
	Calcium Nitrate	NA				
	Cuprous Chloride	NA				
	EH-2001	NA				

General Pest Target	IRAC/HRAC/ FRAC Putative mechanism of action (includes all MOAs for all chemicals 1998-2017 set)	Chemical Class/AI	MOA TARGET SITE	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA with a definitive and/or limit test	Total Number of chemicals IRAC/HRAC/ FRAC have assigned to the MOA without a definitive and/or limit test	Total Number of Chemicals
	Oxysilver Nitrate	NA				
	Potassium tri-iodide	NA				
	S-Dimethenamid	NA				
	Sodium nitrite	NA				
	Tepraloxydim	NA				
	Zona-Stat	NA				
	Demiditraz	Pesticide				
	Forchlorfenuron	Plant Growth Regulator				
	PT807 (Ecolyst)-HCl	plant growth regulator				
	VCD and Triptolide	rodent contraceptive				
	alpha-Chlorohydrin	Rodenticide				
	Dimethyl disulfide	Soil Fumigant				