**From:** Charles Smith
**To:** Rowland, Grant
**Cc:** Catherine Adcock; Dunbar, Anwar; Tanya Clegg
**Subject:** RE: Bicyclopyrone. Final Toxicology DERs
**Date:** Tuesday, April 21, 2015 8:22:58 AM

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Hi Grant

any luck in locating DERs ...

if you guys are having issues popping into CIRCA would it be possible to just attach them to an e-mail and send them northward ?

Thanks !

From: "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>
To: Charles Smith <Charles.Smith@hc-sc.gc.ca>
Cc: Catherine Adcock <Catherine.Adcock@hc-sc.gc.ca>, "Rowland, Grant" <Rowland.Grant@epa.gov>, Tanya Clegg <tanya.clegg@hc-sc.gc.ca>
Date: 2015-04-01 09:56 AM
Subject: RE: Bicyclopyrone. Final Toxicology DERs

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Hello Charles. The DERs were finished and submitted into our databases here. I can't get back into Circa now, so perhaps my product manager Grant Rowland can best advise us on how to get you the documents.

Anwar Y. Dunbar, Ph.D., Pharmacologist
Risk Assessment Branch 1
The Human Health Effects Division/ The Office of Pesticide Programs
1200 Pennsylvania Ave, NW
Washington, DC 20460

"Mastery of any cognitive skill requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

**From:** Charles Smith [mailto:Charles.Smith@hc-sc.gc.ca]
**Sent:** Wednesday, April 01, 2015 9:38 AM
**To:** Dunbar, Anwar
**Cc:** Catherine Adcock; Rowland, Grant; Tanya Clegg
**Subject:** Re: Bicyclopyrone. Final Toxicology DERs

Hi Anwar

happy new month :)

just doing my job as a "Professional Pesterer" ...

any updates on the status on the DERs for your favourite active ingredient ...

Thanks !

From: "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>
To: Charles Smith <Charles.Smith@hc-sc.gc.ca>, "Rowland, Grant" <Rowland.Grant@epa.gov>
Cc: Catherine Adcock <Catherine.Adcock@hc-sc.gc.ca>, Tanya Clegg <tanya.clegg@hc-sc.gc.ca>, Terri A Stewart <terri.a.stewart@hc-sc.gc.ca>
Date: 2015-03-09 08:51 AM
Subject: Re: Bicyclopyrone. Final Toxicology DERs both Chronic and Acute

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Hello Charles. I apologize for not getting back to you. The DERs are in their final stage of review. I estimate that I'll have them done by the end of this month.

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**From:** Charles Smith <Charles.Smith@hc-sc.gc.ca>
**Sent:** Monday, March 9, 2015 8:48 AM
**To:** Rowland, Grant; Dunbar, Anwar
**Cc:** Catherine Adcock; Tanya Clegg; Terri A Stewart
**Subject:** RE: Bicyclopyrone. Final Toxicology DERs both Chronic and Acute

Hi Guys

I understand you guys had a bit of weather down there in Washington over the last couple of days, I hope you we able dig yourselves out and hook up the dog sledge team :)

I had sent the below e-mail a few weeks back and I got an out of office notice from you ...

I was hoping you had some time to check out the status/progress of the various Tox DERs including the Acute TOX DERs ...

please feel free to contact Tanya and Cathy directly if that would be the most efficient way to get the DERs up north ...

Thanks !

From: Charles Smith/HC-SC/GC/CA
To: "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>, "Rowland, Grant" <Rowland.Grant@epa.gov>
Cc: Catherine Adcock <Catherine.Adcock@hc-sc.gc.ca>, Tanya Clegg <tanya.clegg@hc-sc.gc.ca>, "Terri A Stewart" <terri.a.stewart@hc-sc.gc.ca>

Date: 2015-02-16 07:25 AM
Subject: RE: Bicyclopyrone. Final Toxicology DERs both Chronic and Acute

---

Hi Grant and Anwar

Grant recently indicated that there was movement on the EPA Bicyclopyrone review, so that is good news ...

as for the Chronic Toxicology DERs that Anwar is working on, can you guys let us know if they are closer to completion and, if yes, a possible time when the Chronic DERs may be ready for PMRA to get a copy ...

as Grant noted below, it appears DERs are NOT created for the Acute Tox reviews ...

Tanya and Cathy, can you and I have a chat to determine the best path forward for the Acute DERs ...

Anwar, can you please provide your updates to Tanya and Cathy as well as myself when you have determined a possible date for completion of the Chronic DERs ...

Thanks !

Charles Smith

Senior science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: "Rowland, Grant" <Rowland.Grant@epa.gov>

To: Charles Smith <Charles.Smith@hc-sc.gc.ca>
Cc: Catherine Adcock <Catherine.Adcock@hc-sc.gc.ca>, "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>, Tanya Clegg <tanya.clegg@hc-sc.gc.ca>, "Terri A Stewart" <terri.a.stewart@hc-sc.gc.ca>

Date: 2015-01-06 04:17 PM
Subject: RE: Bicyclopyrone. EPA Accepted Use Pattern, Final Toxicology Reviews and TOXSAC Info

---

Hello Charles,

Happy New Year to you as well. I hope it has indeed started off well for you.

As for the Acute Tox reviews, you are correct in noting that Anwar and our Health Effects Division are only in charge of the Chronic toxicology reviews. As for the Acute tox reviews, those are assigned to our Toxicology Review branch (now CITAB) here in the Registration Division. As for the final reviews themselves, they have been completed and posted to CIRCABC (DEC 15, 2014). The DERs are a different story. Historically, It appears as though our acute tox teams do not create DERs for their reviews because they do not pertain to what actually come from the acute tox studies.

If it is the reviews you are looking for, and you are unable to locate them in CIRCABA, then please let me know and I can send you a copy and perhaps they will hold all the information you are looking for. If it is in fact DERs that you want, then we can discuss the best way for you to get the information you need knowing that no DERs are created for acute tox reviews.

-Grant

*Grant Rowland*

*Herbicide Branch*

*Registration Division*

*Office of Pesticide Programs*

*703-347-0254*

**From:** Charles Smith [mailto:Charles.Smith@hc-sc.gc.ca]
**Sent:** Tuesday, January 06, 2015 10:40 AM
**To:** Rowland, Grant
**Cc:** Catherine Adcock; Dunbar, Anwar; Isbell, Diane; Tanya Clegg; Terri A Stewart
**Subject:** RE: Bicyclopyrone. EPA Accepted Use Pattern, Final Toxicology Reviews and TOXSAC Info

Hi Grant

I hope you had a Merry Christmas and followed that up with a Happy New Year ...

alas, I fear it is now time to return back to our collective labours ...

as a clarification to our request for the Toxicology DERs and such, it has been noted that the Acute Toxicology studies may not have been under Anwar's review ...

if the Acute Toxicology DERs were, in fact, not under Anwar's review, can you please inform the appropriate EPA evaluator that PMRA would like to have the Acute Toxicology DERs as well ...

Thanks !

Charles Smith

Senior science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: "Rowland, Grant" <Rowland.Grant@epa.gov>
To: Charles Smith <Charles.Smith@hc-sc.gc.ca>, "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>
Cc: Tanya Clegg <tanya.clegg@hc-sc.gc.ca>, Catherine Adcock <Catherine.Adcock@hc-sc.gc.ca>, "Isbell, Diane" <Isbell.Diane@epa.gov>, "Terri A Stewart" <terri.a.stewart@hc-sc.gc.ca>
Date: 2014-12-15 12:09 PM
Subject: RE: Bicyclopyrone. EPA Accepted Use Pattern, Final Toxicology Reviews and TOXSAC Info

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Charles,
My apologies for the slow response. I'll work on getting you everything you requested ASAP.

-Grant

*Grant Rowland*
*Herbicide Branch*
*Registration Division*
*Office of Pesticide Programs*
*703-347-0254*

**From:** Charles Smith [mailto:Charles.Smith@hc-sc.gc.ca]
**Sent:** Monday, December 15, 2014 11:19 AM
**To:** Rowland, Grant; Dunbar, Anwar
**Cc:** Tanya Clegg; Catherine Adcock; Isbell, Diane; Terri A Stewart
**Subject:** RE: Bicyclopyrone. EPA Accepted Use Pattern, Final Toxicology Reviews and TOXSAC Info

Hi Guys

sorry to keep bugging you guys on this ... but regulation sleeps for no person and we need to tie up the loose ends for this project ...

Anwar, I'm hoping you have a possible date for the completion of your DERs, also, PMRA can't seem to find the information which was presented at the TOXSAC for this active ...

can you check and see if the TOXSAC info was sent and just got lost or if the TOXSAC was not sent to PMRA ...

based on what you find, can you either:
1. forward/re-send the perviously sent e-mail with the TOXSAC information or
2. please send the TOXSAX information directly to Tanya and Cathy ...

Grant, sorry to keep bugging you on this, if you know who is taking this project over as a result of your re-organization, I would be more than happy to bug that person :)

Thanks !

Charles Smith

Senior  science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: Charles Smith/HC-SC/GC/CA
To: "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>, "Rowland, Grant" <Rowland.Grant@epa.gov>
Cc: Tanya Clegg/HC-SC/GC/CA@HWC, Catherine Adcock/HC-SC/GC/CA@HWC
Date: 2014-12-08 10:33 AM
Subject: RE: Bicyclopyrone. EPA Accepted Use Pattern and Final Toxicology Reviews

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Hi Guys

I hope you both made it through your Thanksgiving and were able to take advantage of the "Black Friday" sales without getting trampled trying to get a plasma TV :)

so , I am just following up on the Bicyclopyrone festivities ...

Anwar, have you been able to come up with a possible date for completion of the final DERs ...

I am asking because PMRA is finalising our decision and we fully expect the applicant to want to have the documents i.e. DERs on which PMRA based the regulatory decision ...

I have found that our Canadian applicants are more than happy to point out the folly and foibles in some of our decisions ... not sure if the American company's are nearly as "helpful" :)

also, Grant had indicated there was a re-organization going on and that he was off the Bicyclopyrone case ...

do you guys know who I am now allowed to officially pester in EPA RD on the Bicyclopyrone project

Thanks !

Charles Smith

Senior  science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>
To: Charles Smith <Charles.Smith@hc-sc.gc.ca>
Cc: "Rowland, Grant" <Rowland.Grant@epa.gov>
Date: 2014-11-20 02:04 PM
Subject: RE: Bicyclopyrone. EPAQ Accepted Use Pattern and Final Toxicology Reviews

---

Hello Charles. I am working about incorporating PMRA and AMPVA's comments into the final DERs right now. I will confer with Grant about my deadline for having the final drafts finished and compiled for you all.

Anwar Y. Dunbar, Ph.D., Pharmacologist
Risk Assessment Branch 1
The Human Health Effects Division/ The Office of Pesticide Programs
1200 Pennsylvania Ave, NW
Washington, DC 20460

"Mastery of any cognitive skill requires roughly 10,000 hours of practice"- Malcolm Gladwell, Author of the book Outliers

**From:** Charles Smith [mailto:Charles.Smith@hc-sc.gc.ca]
**Sent:** Thursday, November 20, 2014 1:16 PM
**To:** Dunbar, Anwar
**Cc:** Rowland, Grant
**Subject:** RE: Bicyclopyrone. EPAQ Accepted Use Pattern and Final Toxicology Reviews

Hi Guys

first, Anwar, thank you very much for the information provided below, it was very helpful to our PMRA folks ...

the PMRA is wrapping up our review of this active and as part of that review would like to tie up a few loose ends :) ...

just a couple of questions ...

1. is EPA in a position to let PMRA know what the accepted use pattern of the Bicyclopyrone products will be and if MRLs have been set, I know you were going for a PRIA of Feb, 2015 so you may not have all the decisions made but it never hurts to ask :) ...

2. Anwar, in terms of the final Detailed Review Documents, I know that because PMRA and EPA had kind of parted ways there may not have been discussions involving PMRA about the incorporation of the

PMRA secondary comments but were you able to generate some type of "final" document which captured the secondary comments from PMRA and Australia ? If yes, could you let me know where to find them so we can have a record of the cooperation we did have for this GJR ...

Thanks !

Charles Smith

Senior science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: "Dunbar, Anwar" <Dunbar.Anwar@epa.gov>
To: Charles Smith <Charles.Smith@hc-sc.gc.ca>, "Rowland, Grant" <Rowland.Grant@epa.gov>
Cc: Catherine Adcock <Catherine.Adcock@hc-sc.gc.ca>, Tanya Clegg <tanya.clegg@hc-sc.gc.ca>
Date: 2014-11-04 03:39 PM
Subject: RE: Bicyclopyrone. PMRA Endpoints

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Hello Charles. I apologize for just now getting back to you, but things have been quite busy here and we have just finished our own assessment. Since the last time we spoke, there were extensive talks with Syngenta about the effects in their Himalayn rabbit studies. They sent us materials which our product manager, Grant Rowland just informed me that he passed on to you all. This information contributed to our weight of evidence and endpoint selection. The endpoints we selected are below. Let me know if you have questions. It seems that we agree on the chronic dietary endpoint and the lack of an acute endpoint for the general population. After our discussions with Syngenta and internal discussions within our own ToxSAC, it was decided that many of the effects at lower doses in the Himalayan rabbit studies weren't justifiable for setting LOAELs and we thus went with the New Zealand White Rabbit study for our acute endpoint for females 13-49, dermal and inhalation. See the table below:

**Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Bicyclopyrone for Use in Dietary Human Health Risk Assessments.**

| Exposure/ Scenario | POD | Uncertainty/FQPA Safety Factors | RfD, PAD, LOC for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Acute | | | | |

| | | | | |
|---|---|---|---|---|
| Dietary (General Population, including Infants and Children) | No endpoint attributable to a single dose and appropriate for the U.S. general population was seen in the bicyclopyrone toxicological database; therefore, an acute dietary point of departure for the general U.S. population was not established. | | | |
| Acute Dietary (Females 13-49 years of age) | LOAEL = 10 mg/kg/day | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF /$UF_L$ = 10X | Acute RfD = 0.01 mg/kg/day<br>aPAD = 0.01 mg/kg/day | **Prenatal Developmental Study (New Zealand White rabbits)**<br>Developmental LOAEL = 10 mg/kg bw based on skeletal variations (the appearance of the 27th presacral vertebrae) |
| Chronic Dietary (All Populations) | LOAEL = 0.28 mg/kg/day | $UF_A$ = 10X<br>$UF_H$ = 10X<br>FQPA SF/$UF_L$= 10X | Chronic RfD = 0.00028 mg/kg/day<br>cPAD = 0.00028 mg/kg/day | **Carcinogenicity (rat)**<br>LOAEL = 0.28/0.35 mg/kg/day (M/F) based on a dose dependent increase in the incidence of opaque eyes and corneal damage in both sexes compared to controls, an increased incidence of thyroid follicular hyperplasia in males, and an increased incidence of chronic progressive nephropathy in the kidneys of males. |
| Cancer (oral, dermal, inhalation) | Classification: "Suggestive evidence of cancer" based on the presence of rare ocular tumors in male rats. Quantification of bicyclopyrone's carcinogenic potential is not required. The CARC recommended using a non-linear approach (i.e., reference dose (RfD)) that will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to bicyclopyrone. | | | |

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. 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). $UF_L$ = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose.

**Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Bicyclopyrone for Use in Occupational Human Health Risk Assessments.**

| Exposure/ Scenario | POD | Uncertainty Factors | LOC for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|---|
| Dermal Short- (1-30 days) and Intermediate-Term (1-6 months) | LOAEL = 10 mg/kg/day<br>DAF = 20.44% [1] | $UF_A$ = 10X<br>$UF_H$ = 10X<br>$UF_L$ = 10X | Occupational LOC for MOE = 1000 | **Prenatal Developmental Study (New Zealand White rabbits)**<br>Developmental LOAEL = 10 mg/kg bw based on skeletal variations (the appearance of the 27th presacral vertebrae) |
| Inhalation Short- (1-30 days) and | LOAEL = 10 mg/kg/day | $UF_A$ = 10X<br>$UF_H$ = 10X | Occupational LOC for MOE = 1000 | **Prenatal Developmental Study (New Zealand White rabbits)**<br>Developmental LOAEL = 10 mg/kg bw based on |

| | | | | |
|---|---|---|---|---|
| Intermediate-Term (1-6 months) | | $UF_L$ = 10X | | skeletal variations (the appearance of the 27th presacral vertebrae) |
| Cancer (oral, dermal, inhalation) | Classification: "Suggestive evidence of cancer" based on the presence of rare ocular tumors in male rats. Quantification of bicyclopyrone's carcinogenic potential is not required. The CARC recommended using a non-linear approach (i.e., reference dose (RfD)) that will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to bicyclopyrone. | | | |

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. 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). $UF_L$ = use of a LOAEL to extrapolate a NOAEL. MOE = Margin of Exposure. LOC = Level of Concern.

[1] Dermal-absorption factor derived from MRID 47842239.

**From:** Charles Smith [mailto:Charles.Smith@hc-sc.gc.ca]
**Sent:** Tuesday, October 21, 2014 10:20 AM
**To:** Dunbar, Anwar; Rowland, Grant
**Cc:** Catherine Adcock; Tanya Clegg
**Subject:** Re: Bicyclopyrone. PMRA Endpoints

Hi Anwar and Grant

sorry to be a pest but I was wondering if you had been able to look at the our e-mails below and would be able to help us out with your input ...

if you are unsure of what we are requesting, please feel free to give myself or Tanya an e-mail or a call ...

if you guys are are still discussing your position and haven't come to a conclusion that's cool as well ...

either way, could you give us a guestimate as to when you may be able to respond ...

we are getting close to our decision target date and would like to include your comments and ideas in our decision making process ...

Thanks !

Charles Smith

Senior science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: Charles Smith/HC-SC/GC/CA

To: "Rowland, Grant" <Rowland.Grant@epa.gov>, Dunbar.anwar@epa.gov

Cc: Catherine Adcock/HC-SC/GC/CA@HWC, Tanya Clegg/HC-SC/GC/CA@HWC

Date: 2014-10-14 08:36 AM
Subject: Re: Bicyclopyrone. PMRA Endpoints

---

Hi Anwar and Grant

PMRA is in the process of establishing end points for this active ...

as part of our review, we would like to include the EPA input/response to the questions presented below which are based on the EPA TOXSAC ...

PMRA is targeting December-ish 2014 (which I believe is close to EPA target date) for the completion of our review so your input/response to the below questions would be very much appreciated ...

Tanya is lead tox evaluator for this active in the PMRA and if you would like to chat with her, she can be reached directly at **613-736-3911** ...

Thanks !

Charles Smith

Senior science coordination officer / Pest Management Regulatory Agency
Health Canada / Government of Canada
charles.smith@hc-sc.gc.ca / tel (613) 736-3625

From: Tanya Clegg/HC-SC/GC/CA

To: Dunbar.anwar@epa.gov

Cc: Charles Smith/HC-SC/GC/CA@HWC, Catherine Adcock/HC-SC/GC/CA@HWC

Date: 2014-10-06 10:36 AM
Subject: Bicyclopyrone

Anwar,

Subsequent to your ToxSac for Bicyclopyrone, we revisited our endpoints. Please see the comparison table of endpoints below.

**Table 1**. Toxicological Endpoints for Bicyclopyrone

| Endpoint | PMRA | EPA |
|---|---|---|
| ARfD (gen. pop) | 2.0 mg/kg bw/d from NOAEL of 200 mg/kg bw/d (acute neurotoxicity study)<br>CAF 100[a] | Not required |
| ARfD (♀ 13-49) | 0.001 mg/kg bw/d from NOAEL (malformations) of 1 mg/kg bw (co-critical rabbit developmental studies)<br>CAF 1000[b] | Proposed 0.01 from NOAEL of 1 mg/kg bw (co-critical rabbit developmental studies.<br>100X |
| ADI (gen. pop) | 0.001 mg/kg bw/d from a LOAEL of 0.28 mg/kg bw/d (2-year chronic/carcinogenicity study in rats)<br>CAF 300[c] | 0.00028 mg/kg bw/d from a LOAEL of 0.28 mg/kg bw/d (2-year chronic/carcinogenicity study in rats)<br>1000X |
| Short/Intermediate Dermal | NOAEL of 1 mg/kg bw/d (co-critical rabbit developmental studies)<br>MOE 1000 | Proposed NOAEL of 1 mg/kg bw/d (co-critical rabbit developmental studies)<br>100X |
| Short/Intermediate Inhalation | NOAEL of 1 mg/kg bw/d (co-critical rabbit developmental studies)<br>MOE 1000 | Proposed NOAEL of 1 mg/kg bw/d (co-critical rabbit developmental studies)<br>100X |

[a] PCPA reduced to 1-fold

[b] PCPA maintained at 10-fold

[c] UF LOAEL 3-fold

We have decided to maintain the originally proposed endpoints for the ARfD and occupational endpoints, based on the missing ureter and kidney (a malformation) in the rabbit developmental study. During ToxSac, the EPA indicated that, since this finding was not dose related, it was not considered treatment related. Syngenta had indicated that the finding was congenital and therefore not treatment related. The PMRA felt there was not enough evidence to discount a treatment related find based on it being a congenital disorder as there was no evidence of dams with missing kidney/ureters in one study and in the study with 2

dams with missing kidney/ureter, the fetuses of the affected dams were not affected. Additionally, while there is no dose response, there is a decreased number of fetuses at the high dose which could affect the appearance of a dose response and the dose response for tyrosemia in the database is also flat. We are concerned that although the only unilateral missing kidney/ureter was observed in rabbits, it could manifest in humans bilaterally. **Does the EPA have any further thoughts with regard to this malformation?**

Syngenta notified us that you have requested several pieces of information regarding septal effect in the rabbit developmental toxicity studies. **Please share Syngenta's response with us when you receive it.**

We are also wondering if any of the tox endpoints have been finalized since the ToxSac? As indicated in the table above, three of the endpoints were proposed pending further investigation into the septal effects. If/when the endpoints are determined, could you please share your final endpoints?

Thank you for your time and consideration,

Tanya