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**From:** Papineni, Sabitha (S) [SPapineni@dow.com]  
**Sent:** 12/4/2017 11:07:09 PM  
**To:** Beck, Nancy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=168ecb5184ac44de95a913297f353745-Beck, Nancy]; Schweer, Greg [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4fe412a2024b4f548eeb02e7e931f484-GSchweer]  
**CC:** Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]; Hanley, Mary [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58e0d3d52d424d45ae88e4386ae4f8dd-Hanley, Mary]; Juberg, Daland (DR) [DRJuberg@dow.com]  
**Subject:** RE: PMN meeting  
**Attachments:** DAS\_PMN\_Testing\_Justification\_Final.docx

**Importance:** High

Thank you very much Nancy.

Dear Greg,

Appreciate your time and consideration on this issue.

Would there be an opportunity to discuss this further and to reevaluate the testing requirements with OPPT?

As Daland mentioned, the testing requirements of the PMNs were previously agreed on by DOW. However, we do not agree with the reasons driving the

requirement of an OECD 422 (the reproductive and developmental screening study) via inhalation). OPPT stated that they noted changes in pup body weights at the highest dose of 300 mg/kg/day with the analog (parent Rinskor active) in the two generation reproduction and they consider the changes to be adverse and thus PMNs could have the potential to induce the same. However, we disagree with OPPT's assessment of pup body weight changes and furthermore it also contrasted with HED's assessment of the data for Rinskor active. In Sep 2017 when granting an unconditional registration under FIFRA for Rinskor HED concluded that there are no treatment related effects to the parent or offspring at any dose levels tested. In addition, based on lack of toxicity for Rinskor, no point of departures were selected and no quantitative risk assessments were conducted.

Additional justification has been described in detail in the attached document (including exposure potential) for your review. Please note that OECD 422 will use significant number of rats, a total of ~800 rats including offspring.

Regarding the other endpoint of concern for OPPT, the skin sensitization- Rinskor is a weak dermal sensitizer and the registrant would be willing to assign sensitization classification for PMNs since appropriate risk mitigation measures such as standard OSHA required PPE are already in place for manufacturing workers. Thus, we requests a waiver for conducting an LLNA with the PMNs.

Based on this rationale and the discrepancy noted in the review of two-gen data between OPPT and HED based on which an OECD 422 was required, we would request OPPT for an opportunity to discuss this further and to reevaluate the testing requirements.

Thanking you,

**Sabitha Papineni, DVM, Ph.D**

**Senior Toxicologist**

Human Health Assessment

Regulatory Sciences and Government Affairs

Dow AgroSciences

9330 Zionsville Rd

Indianapolis, IN-46268

Ph. Ex. 6  
Fax. 317-337-4880  
E-mail: spapineni@dow.com

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**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]  
**Sent:** Monday, December 04, 2017 12:30 PM  
**To:** Juberg, Daland (DR) <DRJuberg@dow.com>  
**Cc:** Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>; Papineni, Sabitha (S) <SPapineni@dow.com>; Schweer, Greg <Schweer.Greg@epa.gov>  
**Subject:** RE: PMN meeting

Thanks Daland.

Sabitha-

Since the time when you agreed to the order, have you had any discussions with Greg Schweer regarding the testing concerns?

If not, I suggest you have your first meeting with Greg. I have cc'd him above.

Regards,  
Nancy

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Nancy B. Beck, Ph.D., DABT  
Deputy Assistant Administrator, OCSPP  
P: 202-564-1273  
M: Ex. 6  
[beck.nancy@epa.gov](mailto:beck.nancy@epa.gov)

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**From:** Juberg, Daland (DR) [mailto:DRJuberg@dow.com]  
**Sent:** Monday, December 4, 2017 7:25 AM  
**To:** Beck, Nancy <Beck.Nancy@epa.gov>  
**Cc:** Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>; Papineni, Sabitha (S) <SPapineni@dow.com>  
**Subject:** RE: PMN meeting

Hi Nancy – yes, we are seeking a discussion on testing that was previously requested/agreed to – I am now going to simply bring in Sabitha Papineni to this discussion and ask her to liase with you and EPA directly on next steps. Thanks for your collective efforts.

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**From:** Beck, Nancy [mailto:Beck.Nancy@epa.gov]  
**Sent:** Friday, December 01, 2017 7:41 PM  
**To:** Juberg, Daland (DR) <DRJuberg@dow.com>  
**Cc:** Bolen, Derrick <bolen.derrick@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>  
**Subject:** RE: PMN meeting

Daland,  
Apologies for the delay in getting back to you.  
Staff are telling me that these PMNs are ones which EPA has approved and Dow has already commenced production. Is that correct?  
Are you seeking a discussion on testing that was previously agreed to?

Regards,

Nancy

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Nancy B. Beck, Ph.D., DABT  
Deputy Assistant Administrator, OCSPP  
P: 202-564-1273  
M: Ex. 6  
[beck.nancy@epa.gov](mailto:beck.nancy@epa.gov)

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**From:** Juberg, Daland (DR) [<mailto:DRJuberg@dow.com>]  
**Sent:** Thursday, November 16, 2017 8:51 AM  
**To:** Beck, Nancy <[Beck.Nancy@epa.gov](mailto:Beck.Nancy@epa.gov)>  
**Cc:** Bolen, Derrick <[bolen.derrick@epa.gov](mailto:bolen.derrick@epa.gov)>  
**Subject:** RE: PMN meeting

Nancy, Derrick – this is the high-level situation for your review and suggested next steps. I left the two PMN identifiers on Nancy’s VM. Below summary is from the lead toxicologist on the team and based on your recommendation for next steps (30 min initial call, F2F meeting, etc.), I will then bring her/the team into this and let them lead from here with EPA. Many thanks.

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OPPT has requested the following testing for Rinskor PMNs:

- 1) Genotox (Ames and micronucleus)
- 2) Dermal Sensitization
- 3) OECD 422 *via* inhalation with TK and or micronucleus (this is repeat dose toxicity combined with reproductive and developmental screening which requires 800 rats) (only for one of the intermediate- depending on the results, it will be triggered for other intermediate).

DAS rationale for not requiring the testing for PMNs:

**A) Lack of Hazard potential for PMNs:**

- 1) Rinskor (a new rice herbicide and the parent active) is considered as an appropriate surrogate or analog for these PMNs for read-across.
  - Rinskor (Florpyrauxifen benzyl) was granted unconditional registration under FIFRA as rice herbicide in September, 2017.
  - It was also granted a reduced risk designation based on its low human health risk profile.
  - Based on lack of toxicity for Rinskor, no points of departure were selected and no quantitative risk assessments were conducted.
- 2) The basis to ask for OECD 422 was OPPT’s evaluation of Rinskor two-generation reproduction study results indicating that the changes in pup body weights at the highest dose of 300 mg/kg/day. However, this assessment is in contrast to what HED has concluded suggesting that there are no treatment related effects to the parent or offspring at any dose levels tested with Rinskor.
- 3) Rinskor is a weak dermal sensitizer, DAS is willing to take sensitization classification for PMNs as appropriate risk mitigation measures such as standard OSHA required PPE are already in place for manufacturing workers.

**B) Lack of Exposure Potential for PMNs:**

- 1) Both PMNs have low vapor pressure reducing exposure potential via inhalation
- 2) Gastro plus Simulation and EPA’s MPPD models consistently predicted a lower inhalation absorption for both PMNs.
- 3) Both PMNs are predicted to exhibit sublinear kinetics similar to Rinskor.
- 4) Most importantly, it is a **closed manufacturing system** reducing exposure to workers and
  - a. furthermore, workers wear PPE that minimizes both dermal and inhalation exposures
    - i. Supplied air breathing hood,
    - ii. Tyvek or PVC Suit,
    - iii. nitrile under neoprene gloves taped to suit

**C) Pesticide intermediate is the only use for the PMNs:**

- 1) Patent protected until 2032 and beyond
- 2) Generic production unlikely for 12-15 years due to barrier to entry with data compensability under FIFRA statues
- 3) Complex synthetic route and no closely related analogs

As per Lautenberg New Chemical Safety act requirement under Section 4 testing of chemicals by manufacturers, importers, and processors is only required "**where risks or exposures of concern are found**".

**Based on the above rationale for Rinskor PMN substances, since there is no hazard or exposure potential, there is no Risk, DAS believes Rinskor PMN substances do not trigger the criteria for any additional testing.**

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**From:** Beck, Nancy [mailto:[Beck.Nancy@epa.gov](mailto:Beck.Nancy@epa.gov)]  
**Sent:** Wednesday, November 15, 2017 9:00 AM  
**To:** Juberg, Daland (DR) <[DRJuberg@dow.com](mailto:DRJuberg@dow.com)>  
**Cc:** Bolen, Derrick <[bolen.derrick@epa.gov](mailto:bolen.derrick@epa.gov)>  
**Subject:** PMN meeting

Daland,  
Got your message and I presume you are referring to a new chemical issue. Happy to have a 30 minute meeting (phone or in person). Derek can help get it on my calendar and if you tell me or him the PMN number we can ensure correct experts attend as well. You may not want to email the PMN number as it may likely be CBI.

If you were referring to something else, just let me know the topic.  
Regards,  
Nancy

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Nancy B. Beck, Ph.D., DABT  
Deputy Assistant Administrator  
Office of Chemical Safety and Pollution Prevention  
P: 202-564-1273  
M: Ex. 6  
[beck.nancy@epa.gov](mailto:beck.nancy@epa.gov)