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MEMORANDUM

TO: Jennifer Teerlink, PhD,
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FROM: Shelley DuTeaux, PhD MPH, Chief
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On behalf of the Fipronil Risk Assessment Project Team: Leona D. Scanlan, PhD, (former member), Svetlana E. Koshlukova, PhD, Andrew L. Rubin, PhD DABT, Anna Kalashnikova, PhD, Puttappa Dodmane, PhD, Stephen Rinkus, PhD, Peter N. Lohstroh, PhD, Qiaoxiang Dong, PhD, Brendan Darsie, MPH, Shelley DuTeaux, PhD MPH

DATE: January 17, 2023

SUBJECT: Response to Comments by the US Environmental Protection Agency regarding DPR's 2021 Fipronil Draft Risk Characterization Document

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Background

At the request of the Department of Pesticide Regulation (DPR), the Health Effects Division (HED) of US Environmental Protection Agency's (US EPA) Office of Pesticide Programs reviewed the January 2021 Draft Risk Characterization Document (RCD) for fipronil. HED was asked to comment on a series of charge questions covering the toxicity, hazard identification, exposure and risk characterization. Their comments appeared in a memorandum submitted to DPR on May 18, 2021.

DPR's responses to the comments specific to the toxicity, hazard identification and risk characterization sections of the draft RCD are provided in this document. Responses to the charge questions relating to the exposure assessment appear in a separate memorandum.

DPR sincerely appreciates HED's review. Comments from other regulatory agencies can be helpful in the development of technically complex, science-based regulatory documents.

Responses to Toxicty Charge Questions

DPR Charge Question 1: All critical points of departure (PODs) used in this assessment were established using the parent compound fipronil.

HED Comment: HED agrees with DPR's approach of POD selection based on the parent compound, fipronil.

DPR Response: Comment on this question is noted.

Responses to Hazard Identification Charge Questions

DPR Charge Question 1: The acute oral POD of 0.87 mg/kg/day was based on neurotoxic effects observed in adult rats.

HED Comment: HED agrees with DPR's selection of an endpoint based on an acute neurotoxicity study. However, HED did not use BMD modeling to calculate an acute POD for fipronil. The POD set by HED for acute dietary exposure in all populations is based on the no observed adverse effects level (NOAEL = 2.5 mg/kg/day) established for the acute neurotoxicity study (ACN). The lowest observed adverse effects level (LOAEL = 7.5 mg/kg/day) in the ACN elicited decreased hind leg splay in males at the time of peak effect (7 hours post dose). Uncertainty factors for interspecies extrapolation (10X), intraspecies variation (10X), and an FQPA SF (1X) were applied for the acute dietary assessment.

DPR Response: DPR uses the BMD approach to derive PODs for all data amenable to modeling. BMD takes into account all of the data for a particular effect, and is the preferred approach to resolve statistical uncertainties and identify threshold levels. Specific to the acute neurotoxicity study (Hughes, 1997), the hindlimb splay data in males was suitable for modeling and generated a $BMDL_{10}$ of 0.87 mg/kg/day as the critical oral POD. Using BMD reduced the uncertainty in the acute POD designation, because the model recognized that some level of decreased hindlimb splay at the study NOEL of 2.5 mg/kg/day was treatment-related (i.e., above the normal variation). DPR found further support for the critical acute $BMDL_{10}$ of 0.87 mg/kg/day from the subchronic inhalation toxicity study in rats (Adamo-Trigiani, 1999), which reported clinical signs on day 2 and decreased body weight and food consumption during week 1 at the LOEL of 4.8 mg/kg/day, and set a short-term study NOEL of 0.8 mg/kg/day. The proximity of the experimental value (0.8 mg/kg/day) and the model-derived value ($BMDL_{10}$ of 0.87 mg/kg/day) is a confirmation of the validity of the model. After re-modeling the hindlimb splay dataset with the most recent software, BMDS v 3.2, the updated critical acute oral $BMDL_{10}$ is now 0.77 mg/kg/day with a BMD of 2.09 mg/kg/day.

DPR Charge Question 2: Three repeated dose studies in rats identified PODs lower than the critical acute POD of 0.87 mg/kg/day for effects that could potentially result from acute to short- term exposures. However, DPR did not consider these PODs as appropriate critical values to characterize the risk from acute exposures to humans.

HED Response: HED agrees with DPR's assessment that PODs from the developmental neurotoxicity study, comparative thyroid assay, and chronic toxicity study are not appropriate to characterize the risk from acute exposures to humans.

DPR Response: Comment on this question is noted.

DPR Charge Question 3: PODs from dermal and inhalation studies were not used to establish critical PODs.

HED Response: HED agrees with the selection of dermal and inhalation PODs using oral studies in rats. HED used a similar approach where the route specific dermal (rat and rabbit) and inhalation (rat) studies were not selected for route-specific evaluations because the thyroid, a known target of fipronil, was not completely evaluated in these studies. Additionally, in the case of the inhalation study, the endpoints were not protective of the thyroid effects noted in the database.

DPR Response: Comment on this question is noted.

DPR Charge Question 4: This RCD did not include a cancer risk estimate for fipronil.

HED Response: HED agrees with DPR's approach to access the carcinogenicity of fipronil. The HED Carcinogenicity Peer Review Committee classified fipronil as a possible human carcinogen (Group C), based on statistically significant increases in thyroid follicular cell tumors in male and female rats (V. Dobozy and E. Rinde, TXR 0011616, 07/18/1995). There was no evidence of mutagenicity in the fipronil toxicity database. In addition, there was no concern for cancer from exposure to the photodegradate MB 46513, given the lack of carcinogenic effects in the chronic/carcinogenicity study in rats and negative findings in the mutagenicity studies. HED agrees with the use of a non-linear approach (i.e., cRfD) to adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to fipronil and its metabolites/degradates.

DPR Response: Comment on this question is noted.

Responses to Risk Characterization Charge Questions

DPR Charge Question 1: The target margin of exposure (MOE) was set at 100, reflecting the default assumption that humans are 10-fold more sensitive than animals, and that a 10-fold range of sensitivity exists within the human population.

DPR Charge Question 2: Risks to workers were estimated for short-term, seasonal and annual exposures.

DPR Charge Question 3: Risks to home users were estimated for short-term exposures.

DPR Charge Question 4: Post-exposure risks to child and adult residents were estimated for short-term and seasonal exposures.

HED Response to All Risk Characterization Charge Questions:

Levels of Concern (LOC):
HED has selected different LOCs based on different exposure scenarios. HED's LOC for all short- and intermediate-term residential and occupational scenarios is 30 based on a combination of uncertainty factors for interspecies extrapolation (UFA = 3X), intraspecies variation (UFH = 10X), and the FQPA SF (1X), when applicable. The interspecies uncertainty factor was reduced to 3X to account for the increased sensitivity of rat adults and pups to thyroid hormone perturbation compared to humans. This reduction in the toxicodynamic portion of the interspecies uncertainty factor can be applied to these scenarios only because the PODs are based on thyroid effects, there is no evidence that pregnant female rats, fetuses, or offspring are more sensitive to thyroid perturbations compared to adult males and non-pregnant females, and there were no other systemic effects noted following subchronic exposure at or below the dose level that elicited thyroid toxicity in rat adults and pups. The LOC for all long-term scenarios is 100 based on a combination of uncertainty factors for interspecies extrapolation (UFA = 10X), intraspecies variation (UFH = 10X), and the FQPA SF (1X), when applicable.

DPR Response: The different levels of concern (LOCs) for short- and intermediate-term exposure scenarios reflects the use of different PODs to calculate the risks and the available data in the critical studies to inform the uncertainty factors. Note that DPR's target margin of exposure (MOE) is 100 and HED's LOC is 30. For short-term (1-7 days) exposures to fipronil, DPR selected the acute POD of 0.87 mg/kg/day based on effects in the acute neurotoxicity study in rats (Hughes, 1997). For seasonal (greater than 1 week to one year) exposures, DPR used the subchronic POD of 0.02 mg/kg/day based on effects seen within one year in the chronic toxicity study in rats (Aughton, 1993). Neither study provided data addressing toxicokinetic or toxicodynamic uncertainties between or within species. Therefore, for both exposure durations DPR considered 100 as the appropriate target MOE (the default). In contrast, HED determined that a LOC of 30 was sufficient for short-term and intermediate-term scenarios using toxicodynamic evidence in the comparative thyroid toxicity assay (CTA) in rats, which established a critical POD of 0.3 mg/kg/day (Coder, 2019). DPR derived the maternal and fetal NOELs at 1 and 0.3 mg/kg-day, respectively, from Coder (2019). This is opposite of HED's designations. Regardless, DPR concluded that the thyroid hormone measurements in the CTA were not quantitatively reliable due to failed

ion ratios. Further explanation for this is found in the final RCD. For this reason, DPR did not base the critical POD determinations on Coder (2019).

DPR's target MOE of 100 for all long-term (annual) scenarios was the same as the HED's LOC based on the chronic toxicity study in rats from which both agencies established the same critical chronic POD of 0.02 mg/kg/day.

Exposure and Risk Estimates:
HED's responses above regarding occupational and residential exposure data sources highlight the differences between that used by DPR and the Agency. Therefore, please refer to the 2020 fipronil DRA for a comparison of the resulting occupational and residential handler exposures to the recommended levels of concern, as well as the residential post-application exposures and risks estimated for contact with treated turf and contact with pets treated with fipronil sprays and spot-on products. Due to the differences described relating to the DPR's and HED's usage of exposure data, the exposures and risks estimated by HED differ from those estimated by DPR.

DPR Response: Comment on this question is noted. Separate responses to exposure estimates are found in a separate memo.

References

Adamo-Trigiani, M. 1999. A 28-Day Inhalation Toxicity Study by Nose-Only Exposure of Fipronil Technical (micronized) in the Albino Rat. In *Sumitomo Chemical Company, LTD, Osaka, Japan, Project No. 91087*.

Aughton, P. 1993. M&B 46030: Combined Oncogenicity and Toxicity Study by Dietary Administration to CD Rats for 104 weeks Including a 13 Week Reversibility Period on Completion of 52 Weeks of Treatment. In *Pharmaco-LSR LTD Eye Suffolk, UK. LRS Report 93/RHA432/0166*.

Coder, P. 2019. Fipronil – an oral (dietary) comparative thyroid assay in pregnant, postnatal and fetal Sprague-Dawley rats. In *Fipronil Task Force, LLC, Raleigh, NC, Lab Project ID 00657506*.

Hughes, E. 1997. Fipronil: Neurotoxicity to rats by acute oral administration (including a time to peak effect study). Huntingdon Life Sciences Ltd., Cambridgeshire, PE18 6ES, U.K., RNP 536/973345. (DPR Vol. No. 52062-0387, Record No. 235557).