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# MEMORANDUM

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On behalf of the Imidacloprid Risk and Exposure Assessment Project Team:
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DATE: December 31, 2024

SUBJECT: Response to Comments by the US Environmental Protection Agency regarding DPR's March 2024 Draft Human Exposure Assessment Document and Draft Risk Characterization Document for the Non-Agricultural Uses of Imidacloprid

## I. 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 March 2024 Draft Human Exposure Assessment Document (EAD) and the Draft Risk Characterization Document (RCD) for imidacloprid. HED was asked to comment on a series of charge questions covering toxicity, hazard identification, exposure assessment and risk characterization. HED provided comments in a memorandum submitted to DPR on June 5, 2024.

DPR sincerely appreciates HED's review. Comments from other regulatory agencies can be helpful in the development of technically complex, science-based regulatory documents. When appropriate, HED's comments were incorporated into the final imidacloprid EAD and RCD.

This memorandum summarizes DPR's responses to HED's comments on the charge questions provided by DPR along with the original documents for review. Every effort has been made to directly quote HED's comments, although some may have been condensed for clarity and brevity. Only comments that require additional clarification from DPR or that were considered in the finalization of the imidacloprid RCD or EAD are discussed here. References cited in this memorandum pertain specifically to HED's review and DPR's responses, and may not overlap with those in the draft or final DPR risk and exposure assessment documents.

## II. RESPONSE TO COMMENTS ON DPR CHARGE QUESTIONS

### A. DPR Charge Question: The acute oral point of departure of 5.5 mg/kg/day was based on developmental neurotoxic effects in rat pups.

**HED Comments on Acute Point of Departure:** EPA's review of the Sheets 2001 study found a clear no-observed adverse-effect levels (NOAEL) of 20 mg/kg/day for offspring, which is based on decreased absolute body weights and decreased motor activity at the LOAEL of 55 mg/kg/day for offspring. There were no adverse effects observed in maternal animals (NOAEL = 55 mg/kg/day; the highest dose tested). EPA disagrees with the claims that there are significant brain morphometric changes observed in either of the measurements noted by DPR. The differences in caudate/putamen width and corpus callosum thickness reported by CDPR were observed only at PND 11…

> **DPR Response:** US EPA advanced several arguments regarding DPR's designation of 5.5 mg/kg/day as the critical acute ENEL, which was based on changes in brain morphometric measurements in the caudate-putamen (width) and corpus callosum (thickness) regions in postnatal day 11 animals following in utero and lactational exposure to imidacloprid. These arguments are addressed in sequence below. First, DPR analysis of the brain morphometric data showed that reductions in both caudate-putamen width (6%) and the corpus callosum thickness (27%) in PND 11 female pups were statistically significant. Furthermore, the early life reductions appear to have been preserved, at least to some extent (2–7%) on PND 75. In any case, reductions in brain dimensions detected early in postnatal life can, arguably, have consequences for the neurological development of the organism.

**HED Comment, continued:** …The differences in caudate/putamen width and corpus callosum thickness reported by CDPR were observed only…in female pups…

> **DPR Response:** DPR does not find gender selectivity a reason to minimize an effect, particularly in view of the myriad physiological differences, including differences in brain anatomy, that exist between males and females both during and after development.

**HED Comment, continued:** …[T]he difference…was observed only at the highest dose…

> **DPR Response:** The effect on caudate-putamen width was observed only at the highest dose because investigators chose to only measure that outcome at the highest dose versus controls. This, therefore, necessitated the calculation of the ENEL of 5.5 mg/kg/day by applying a LOEL-to-NOEL extrapolation factor of 10.

**HED Comment, continued:** … EPA notes that this difference in the corpus collosum was not observed at study termination (27% for PND 11 vs 7% at termination) reflecting a lack of temporal concordance…

**DPR Response:** While it is true that the magnitude of the decrease in corpus callosum thickness was not as great on PND 75 (7% reduction, not statistically significant) as on PND 11 (27%, $p<0.01$), the trend in the reduction in corpus callosum thickness likely occurred at both time points. The lack of statistical significance at the latter point may indicate a partial but not complete reversal of the effect observed at the earlier point, with some animals retaining a larger quantitative reduction. Therefore, the biometric evidence was consistent with at least some degree of a temporal concordance between PNDs 11 and 75.

**HED Comment, continued:** …The observations in the female PND 11 groups showed greater coefficients of variability (CV) than the controls and dosed groups at termination (CVs of 23% and 18% in controls and high dose group, respectively)…

**DPR Response:** Regardless of the magnitude in coefficients of variability, the presence of pairwise statistical significance on PND 11 strongly suggests that the effects on caudate-putamen and corpus callosum morphometries were real. Furthermore, the OPPTS 870.6300 Developmental Neurotoxicity Study Test Guideline requires that wherever morphometric measurements suggest significance at the high dose, then animals from the intermediate and low dose group be examined. (US EPA, 1998). However, the animals from the intermediate and low dose group were not examined in Sheets 2001, thus adding an uncertainty to the dose response evaluation of the morphometric alterations. Even so, in the case of the corpus callosum, observations of reduction in thickness (27%) at the high dose were toxicologically significant.

**HED Comment, continued:** … Based on the totality of this information, EPA determined that there were no adverse brain morphometric changes due to imidacloprid exposures, for any sex or age.

**DPR Response:** To avoid subjective judgement, DPR does not differentiate observed effects in toxicology studies based on their presumed adversity. Instead, DPR considers all treatment related effects, whether upstream or apical, exhibiting biological and/or statistical significance to be suitable for establishing points of departure for risk assessment.

**HED Comment:** DPR noted that their selection of the ENEL of 5.5 mg/kg/day as the critical acute POD was supported by several lines of evidence, listed below. Overall, EPA generally disagrees that any of these points are supportive or relevant to the brain morphometric effects from Sheets 2001, and provides specific comments below:

***1) Decreased brain dimensions are consistent with a CNS effect, as would be expected with a nicotinic acetylcholine receptor agonist.***

**HED Comment:** EPA does not agree with CDPR's conclusions or lines of evidence regarding the morphometric data, as described above. Furthermore, even if the effects were considered adverse, morphometric alterations are unlikely to result from a single dose exposure and the appropriateness of using these effects to derive an acute endpoint needs to be properly characterized and supported.

> **DPR Response:** DPR considers certain developmental responses including changes in brain structural dimensions, as potentially acute when data indicating otherwise are not available. As noted in the comment below and in the agency's recent human health risk assessment for thiamethoxam (US EPA, 2019), HED also considered altered offspring brain morphometrics as appropriate for setting the acute endpoint for this neonicotinoid (US EPA, 2019).

***2) Dietary administration of thiamethoxam (a neonicotinoid like imidacloprid) to pregnant rats resulted in a ~20% decrease in corpus callosum thickness in pups at 299 mg/kg/day.***

**HED Comment:** EPA does not agree that this point supports the adversity of the brain morphometric alterations for imidacloprid. For thiamethoxam, the observed alterations in offspring brain morphometrics were considered adverse only at the high dose of 299 mg/kg/day. Additionally, the magnitude of observed changes for thiamethoxam at this high dose are significantly larger than any observed alterations for imidacloprid at any dose. Finally, adverse effects for a chemical in a given class do not necessarily support that the same type and/or magnitude of effects would be observed across all chemicals within the same class, particularly when the effect is not consistently observed across the class.

> **DPR Response:** The brain structural decreases induced by imidacloprid at the high dose of 55 mg/kg/day, which amounted to 27% for corpus callosum thickness and 6% for caudate-putamen width on PND 11, were comparable in magnitude to the decrements observed with thiamethoxam at 299 mg/kg/day, where the most severe response was a 20% decrease in corpus callosum thickness at termination. Although the LOELs differed, common CNS effects would be expcted for these two chemicals that share structural similarities and that both act as nAChR receptor agonists. Regardless of the chemical or the dose, both DPR and US EPA have recognized brain morphometric changes as an acute developmental effect.

***3) Changes in brain morphometrics were accompanied by decreased pup motor activities and body weights.***

**HED Comment:** As explained above, the morphometric changes at 55 mg/kg/day are not considered adverse by EPA. EPA determined that the only adverse effects noted at 55 mg/kg/day are the decreased pup body weights and locomotor activities.

**DPR Response:** See responses in Comment A.1. regarding DPR's approach to the issue of adversity in toxicology studies.

***5) An acute LD50 study in mice reported clinical signs (labored breathing, decreased motility and tremors) at LOEL of 71 mg/kg/day.***

**HED Comment:** EPA does not agree that the acute mouse study corroborates the altered brain morphometrics. While the acute study in mice does show potential signs of neurotoxicity, acute toxicity studies are used to establish lethality and are not useful for characterizing specific neurotoxic effects. Tremors and staggering gait are clinical signs that may be indicative of neurotoxicity, but do not correlate to alterations in structural changes in central or peripheral nervous systems. Alterations in brain morphology would require multiple and sustained chemical exposures and the imidacloprid metabolism profile shows that the majority of 4 chemical is cleared by 24 hours at 150 mg/kg. Therefore, EPA does not agree that this acute toxicity study supports alterations to brain morphometrics at 55 mg/kg/day in the 2001 Sheets DNT study.

**DPR Response:** DPR considers any study, including acute toxicity studies for lethality determinations, to be suitable as support for critical PODs if they provide sufficient and relevant qualitative or quantitative information. This applies in the case of the acute study in mice, which established an acute POD for clinical signs that was in the range of the acute POD based brain morphometrics. Finally, there is no evidence that alterations in brain morphology require multiple and sustained chemical exposures. As stated in the responses above, both DPR and US EPA have recognized that brain morphometric changes could result from a single or very few exposures during a critical period of the organ development.

***6) Decreased body weights and induction of hepatic mixed-function oxidases (MFO). were observed in a 5-day inhalation study.***

**HED Comment:** While CDPR reports decreased body weight gains in the 5-day inhalation study, EPA does not consider this metric to be adverse under current practices. Overall, it is not clear how this study strengthens the argument that brain morphometric effect in offspring are adverse.

**DPR Response:** See responses in Comment 1.1. regarding DPR's approach to the issue of adverse effects in toxicology studies.

## B. DPR Charge Question(s): The subchronic oral point of departure of 1.0 mg/kg/day was based on developmental neurotoxic effects in rat pups. The subchronic oral point of departure was also used as the critical oral value.

**HED Comments on Subchronic and Chronic Points of Departure:** Following preliminary review of the Patel 2010 study, EPA does not consider the altered negative geotaxis effect adverse. DPR did not identify any other studies to support the negative geotaxis noted in the Patel study and the associated BMD analyses performed. Overall, EPA disagrees with derivation of subchronic or chronic endpoints based on the geotaxis data. The altered negative geotaxis in neonates is not an effect measured within the EPA 870.6300 test guideline and the effect is neither considered adverse or robust, in isolation.

> **DPR Response**: DPR analysis of the negative geotaxis data on PND 10 revealed a dose-dependent increase in the incidence of male pups not climbing uphill (freezing) after completing the 180$^{o}$ turn, which became significantly different from the control at mid and high doses and appropriate for BMD modeling. Even though negative geotaxis is not included in the EPA 870.6300 test guideline, the Patel 2010 study met DPR data acceptance criteria (DPR, 2023). Furthermore, the data showed a clear treatment-related impact on the developing neuromotor and vestibular function. DPR considers this effect to be both robust and supported by other sensitive subchronic and chronic effects (e.g., immunotoxicity, thyroid toxicity, liver toxicity). Responses on the issue of adversity of effects were provided in the previous section.

**HED Comment, continued:** There were no corroborating effects observed at the low- or mid-dose tested in Patel (2010) and there is no biological or statistical support for using a 5% benchmark response (BMR) with this measure.

> **DPR Response:** As described above, the incidences of altered negative geotaxis in PND 10 male pups (3/23, 6/24, 11/23* and 14/23** at 0, 100, 250 and 750 ppm) were dose-dependent and significant at both the mid and high dose. DPR follows the 2012 US EPA BMD guidance recommendation to use a 5% BMR when modeling developmental effects (US EPA, 2012).

**HED Comment, continued:** Furthermore, EPA noted minimal difference from the control group at the low dose (3/23 vs 6/24), and high variability between the controls on different days (comparing PND 5 to PND 10; 12/25 vs 3/23).

> **DPR Response:** Negative geotaxis is not expressed until at least PND 7 or 8 in rats, so it would be non-detectable in most of the pups on PND 5 when the first measurements were made. Indeed, the data on PND 5 showed that about half of the control animals had not yet developed the negative geotaxis response, whereas all but three pups expressed it on PND 10.

**HED Comment, continued:** Additionally, the existence of negative geotaxis in infant rats has been questioned in the scientific community and has been found to be dependent on experimental conditions, such as the types of platforms and inclination angles used. Some studies suggest that if infant rats do exhibit geotaxis, it may actually be in the form of positive geotaxis (e.g., Motz and Alberts 2005). As a result, based on the totality of the data, the geotaxis results from the

Patel (2010) do not provide a robust endpoint for human health risk assessment. At the highest dose tested in Patel (2010), decreased pup body weights and motor activities were observed and this dose is consistent with the effects observed in the 2001 Sheets study.

**DPR Response:** As noted by HED, there are variations in the precise parameters used to define negative geotaxis. However, the test is accepted by the US Collaborative Behavioral Teratology Study Battery and WHO and has often been used in developmental toxicity tests for environmental chemicals, including for pesticides, and in pharmaceutical safety assessment (WHO, 1984; Buelke-Sam, 1987; St Omer *et al.*, 1991; Dam *et al.*, 2000; Moser, 2005; Farag *et al.*, 2006; Acker *et al.*, 2011; Cole *et al.*, 2012; Tanaka, 2012; Lan *et al.*, 2017). As detailed in our responses to HED's Subchronic and Chronic Toxicity comments, DPR considers the geotaxis results to be robust, dose-dependent and statistically significant, and supported by other sensitive subchronic and chronic effects in the imidacloprid database.

## C. DPR Charge Question: Transferable turf residues (TTR) were used for estimating post-application exposure from turf.

**HED Comment:** In response to the EPA's human health DRA and PID, the results of two chemical-specific TTR studies (2016, MRID 49853501; 2020, MRID 51085501) were submitted and reviewed by HED (J. Tyler, D450519, 11-FEB-2019; and 19-APR-2020; D457623). While these are the same TTR studies that DPR considered in their assessment, EPA considered data from all test plots (conducted in CA, GA, and PA) and, determined that the 2020 TTR study (MRID 51085501) is more relevant and accurately represents current residential application practices. Based on these data, EPA recommended the highest predicted residue value of 0.033 $\mu g/cm^2$ (PA plot) be used in future residential and occupational post-application turf assessments for imidacloprid.

**DPR Response:** As detailed in the draft EAD, the registrant-submitted TTR studies by Kroiski (2016) and Veal (2020) both collected samples following application of imidacloprid in California. Using data from either study would allow for the estimation of human exposure to imidacloprid using California-specific data, as preferred by DPR and consistent with recommendations from the National Academy of Sciences (NAS) following its independent peer review of the department's risk and exposure assessment practices (NRC, 2015). Hence, no change has been made to the TTR value.

## D. DPR Charge Question: DPR applied a seventeen percent (17%) dermal absorption rate in its exposure assessment.

**HED Comment:** EPA used the same study that DPR used to calculate its 17% DAF (Odin-Feurtet et al., 2009, EPA MRID 50411201). As described in the DPR Draft Human Exposure

Assessment for Non-Agricultural and Residential Uses of Imidacloprid document, the rate of imidacloprid dermal absorption was calculated by measuring the amount of imidacloprid bound to the stratum corneum after accounting for the amount of imidacloprid directly absorbed into the animal and the amount retained in the external dose site to (11.873% +4.8% = 16.673%). DPR does not specify the time used for its calculation, but the 8- and 24-hour absorption values reported are 17.4% and 16.5%, respectively. Based upon current practices, EPA selected the 5 $\mu g/cm^2$ dose at the 168-hour time point. EPA combined treated and surrounding skin, untreated skin, urine, feces, cage wash, blood, and carcass fractions to determine an absorbed fraction of 4.8%. The stratum corneum (accounting for ~12%) was not included as there was no evidence of movement of the chemical into systemic absorption from the skin layers after washing. As a result, imidacloprid detected in the stratum corneum and associated skin measures was not considered absorbable by EPA, and therefore, not added to the final dermal absorption factor.

> **DPR Response:** Based on HED's comment, the section on dermal absorption factor derivation in the final EAD has been revised. Specifically, among all the monitoring periods at the lowest test dose, there was no significant decrease in the percentage of bound skin residue in the stratum corneum (based on ANOVA followed by Tukey's Honestly Significant Difference (HSD) post-hoc test). This suggests that the bound skin residue may not be available for absorption. Hence, the derivation of the potentially absorbable dose (PAD) was revised to now consist of the percentage of directly absorbed and total at the dose site, equaling 4.823% as appeared in Odin-Feurtet (2009). The rounded-up value of 5% was used to update all dermal exposure values in the final EAD. The resulting risk estimates based on dermal routes of exposure have been similarly updated in the final RCD.

## E. DPR Charge Question: Composition of active ingredients in impregnated pet collars.

**HED Comment:** Since the completion of the 2017 DRA, EPA has reassessed the potential residential exposure and risk from the registered pet collar use, incorporating the results of two chemical- and formulation-specific studies which sought to determine the actual amount of dust material that could release from the Seresto pet collar following mechanical stress, and the fraction of that material containing the active ingredients (flumethrin and imidacloprid) (MRIDs 50140803 and 50140804).

> **DPR Response:** The original assumption of the pet collar formulation exists as half liquid and half solid was based on the lack of formulation-specific data. However, based on the new information provided to DPR by the US EPA (2024), the pesticide registrant has submitted two studies that allow the US EPA to derive a liquid-to-solid (i.e., 0.9971/0.0029) ratio for assessing residential hander exposure from pet collar usage (Jiritschka, 2011; Hammer, 2016; US EPA, 2019). Accordingly, all exposure calculations involving the

assumption of 0.5/0.5 liquid-to-solid ratio have been updated using the experimentally determined liquid-to-solid ratio.

## III. EPA ADDITIONAL ASSESSMENT COMMENTS

(Note: Numbering added for ease of response)

**HED Additional Comment 1.** Transfer Factor for "Pruning, hand": HED notes the discrepancy in the transfer coefficient (TC) used for the "pruning, hand" activity associated with "flowers, cut." According to EPA Policy 3, the recommended TC for this post-application activity is 200 $cm^2$/hr rather than 4,800 $cm^2$/hr. The 4,800 $cm^2$/hr is the recommended TC for the "harvesting, hand" for the same crop group.

**DPR Response:** "Pruning, hand" has been revised in the final EAD to "harvesting, hand" as flower cutting could be interpreted as "harvesting." This will further distinguish the two activities and to ensure that the exposure assessment scope remains on the non-agricultural use of imidacloprid.

**HED Additional Comment 2.** Use of Chemical-specific Dislodgeable Foliar Residue (DFR) Data in Occupational Post-application Assessment: Footnote C states "For use sites without available DFR data, the default DFR (25% of the maximum use rate) was used as a surrogate." It was unclear if this was a generic statement, or if chemical-specific DFR data were available and applied in the risk assessment. EPA requests clarification on whether chemical-specific DFR data were used in the occupational post-application assessment (Table 10 of the EAD) or which specific use scenarios chemical-specific data were applied. Currently, EPA is not aware of chemical-specific data and used default values (25% of the maximum use rate) consistent with EPA's current exposure assessment approaches described in ExpoSAC Policy 3.

**DPR Response:** Footnote "c" in Table 10 in the final EAD has been revised to indicate source of TTR and DFR. Specifically, the residue value for turf grass in the TTR/DFR column is TTR. The TTR value is based on a study by Bayer CropScience (Kroiski, 2016). The highest reported TTR value of 0.656 µg/cm² was adjusted to 0.525 µg/cm² (i.e., 0.656 x 0.4/0.5) using the California maximum application rate of 0.4 lbs AI/acre and the study application rate of 0.5 lbs AI/acre. No imidacloprid-specific dislodgeable foliar residue (DFR) value is available; hence, a default DFR (25% of the maximum use rate) was used as a surrogate. In each scenario, the maximum use rate from the product label is 0.4 lbs AI/acre.

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