DEPARTMENT OF PESTICIDE REGULATION

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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 Imidacloprid Risk and Exposure Assessment Project Team:
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DATE: December 31, 2024

SUBJECT: Response to Comments by the Office of Environmental Health Hazard Assessment on DPR's March 2024 Draft Human Exposure Assessment Document and Risk Characterization Document for Non-Agricultural Uses of Imidacloprid

I. BACKGROUND

At the request of the Department of Pesticide Regulation (DPR), the Office of Environmental Health Hazard Assessment (OEHHA) reviewed the March 2024 Draft Human Exposure Assessment Document (EAD) and the Draft Risk Characterization Document (RCD) for imidacloprid. OEHHA was asked to respond to a series of charge questions covering the hazard identification, exposure assessment, and risk characterization, and provided comments to DPR on June 3, 2024. DPR sincerely appreciates OEHHA's review.

This memorandum summarizes DPR's responses to OEHHA's comments on the draft RCD and EAD. Every effort has been made to directly quote OEHHA's comments, although some are 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 are specific to OEHHA comments or DPR's response, and do not necessarily correspond to those in the draft or final documents. Likewise, every effort has been made to ensure that any references to tables are clear.

II. RESPONSES TO SUMMARY COMMENTS

OEHHA Summary Comment C.4.: Some of the assumptions made in the exposure assessment may lead to an underestimation of exposure. For example, if the EAD applied the transfer coefficient for lawn mowing that is recommended by US EPA for residential exposures (US EPA, 2012), the subsequent dermal exposure would be 10-fold higher. The EAD lacks details to support the approach and data used to derive the turf transfer factor for mowing. OEHHA suggests adding a more detailed rationale for DPR's approach and explaining why it was chosen over the more health protective transfer coefficient recommended by US EPA. As an alternative, OEHHA recommends using the value from US EPA.

DPR Response: With a few exceptions, OEHHA's impression of underestimation of exposure in the draft EAD is due to various typographical errors introduced in the tables. These corrections have been made in the final EAD. Regarding the lawn mowing example cited by OEHHA, the rationale for using the transfer coefficient instead of the US EPA default is now detailed in Table 10 of the final EAD. Specifically, the turf transfer factor for mowing is derived from the US EPA transfer factor of 3700 cm^2/hr scaled by the ratio of exposed surfaces (head 1204 cm^2; neck 233 cm^2; and hands 904 cm^2) to the total body surface area of 17,213 cm^2, i.e., $17{,}213 \times 0.136 \approx 500$. The surface area of the hands is derived from Tables 6-2 and 6-3 of the US Environmental Protection Agency's (US EPA) Exposure Factors Handbook (US EPA, 1997). Scaling the transfer factor allows for consideration of "exposed body surface areas" such as the head, neck, and hands, given that unlike other activities listed in Table 10 of the final EAD, mowing does not involve direct contact with treated surfaces.

III. RESPONSES TO DETAILED COMMENTS

A. Toxicity Evaluation and Risk Assessment

1. Non-cancer Toxicity Evaluation and Point of Departure Determination

b. Dermal Absorption Factor

OEHHA Comment: OEHHA recommends that to calculate the DAF for imidacloprid, the total amount of imidacloprid directly absorbed (the amounts detected in urine, feces, cage wash, cardiac blood, non-treated skin, and carcass) and present at the application site (the amounts detected in treated and surrounding skin) be combined, and the remaining imidacloprid bound in the stratum corneum be excluded. The low dose group data provided the highest calculated DAF of 4.823% for imidacloprid (Appendix I, Table A2). Thus, a DAF of 5% (due to rounding) for assessment of dermal exposure to imidacloprid is supported by the OECD guidance and study data.

DPR Response: US EPA, OEHHA, and the imidacloprid registrant Elanco US, Inc. all noted that DPR's draft assessment was overly conservative in its assumptions of dermal absorption of imidacloprid. Based on these comments and specific recommendations from US EPA, the derivation of the dermal absorption factor has been revised and incorporated into the calculation of dermal exposure estimates in the final EAD and the corresponding risk determinations in the final RCD. To derive its dermal absorption factor (DAF), US EPA used the same registrant-submitted study that DPR used to calculate the initial 17% DAF (Odin-Feurtet et al., 2009, EPA MRID 50411201). Based on current practices, US EPA selected the 5 $\mu g/cm^2$ dose at the 168-hour time point and combined treated and surrounding skin, untreated skin, urine, feces, cage wash, blood, and carcass fractions to determine an absorbed fraction of 4.8%. US EPA did not include the bound dose in the stratum corneum (accounting for ~12%) in the calculation of the DAF, as it found 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 US EPA and was not added to the agency's final DAF for imidacloprid. Accordingly, DPR revised its derivation of the DAF in the final EAD. In considering 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 DPR's independent statistical tests including 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, therefore confirming US EPA's assertion. Hence, DPR's 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.

Finally, in deriving the dermal absorption factor, OEHHA stated that complete absorption is considered to have occurred when at least 75% of the total chemical amount absorbed by the end of the total study period is present in the excreta or systemic compartment before the study mid-point. As such, it appears that OEHHA based its determination of over 85% of the total imidacloprid absorbed by 72 hours in the 168-hour study duration using the 168-hour value as a reference (as presented in Appendix I, Table AI of the OEHHA review document). Whereas, DPR follows the OECD Guidance Notes on Dermal Absorption published by the Organization for Economic Cooperation and Development in 2022 (OECD 2022), which states that 75% of the total chemical absorbed should be based on the material absorbed by the end of the study (material in excreta + exhaled gases + the carcass excluding the application site).

c. General Approaches

OEHHA Comment: The limited acute and subchronic dermal and inhalation studies for imidacloprid do not provide sufficient data to derive critical PODs. Additionally, there are no chronic dermal or inhalation studies available. OEHHA agrees with the use of oral PODs to assess dermal and inhalation exposure to imidacloprid. The draft RCD derives critical toxicity endpoints for only the imidacloprid parent compound. There is limited toxicity data available for imidacloprid metabolites, however the binding data presented in the draft RCD for the primary environmental degradate, desnitro-imidacloprid, suggests this moiety may have a higher affinity for and be a more potent activator of mammalian brain nAChR. As this moiety is included in the dietary and drinking water exposure analysis, OEHHA recommends that DPR provide additional discussion, at least qualitatively, as to how the toxicity of this metabolite may affect risk estimates.

DPR Response: DPR conducted a highly refined Tier 3 acute probabilistic analysis utilizing the extensive residue data available for imidacloprid from the national and state monitoring programs. As recommended from OEHHA's review of the draft RCD, the dietary exposure assessment was expanded in the final RCD to include desnitro-imidacloprid. Following databases searches for additional imidacloprid metabolites and degradates, both imidacloprid urea and olefinic imidacloprid were also included in the final dietary assessment. Monitoring data were available for these three breakdown products of imidacloprid in 6 foods. No monitoring data were available for any other imidacloprid metabolite or degradate, and hence were not included in the final analysis. The impact of including desnitro-imidacloprid, imidacloprid urea and olefinic imidacloprid on the dietary risk estimates is discussed in the Dietary Exposure Assessment Section below (see c. Desnitro-imidacloprid Exposure) and in the Risk Appraisal section in the final RCD (see 2. Dietary Exposure Assessment Appraisal).

d. Acute Toxicity

OEHHA Comment: OEHHA recommends that Patel (2010) be used to derive the acute POD instead of Sheets (2001) for several reasons. First, the two studies have similar protocols and timelines of effects. Both DNT studies exposed rats to imidacloprid technical in the diet beginning at implantation (gestation day, GD, 0) until lactation day (LD) or PND 21. The observed critical effects were evaluated on PND 10 (altered negative geotaxis) in Patel (2010) and on PND 11 (reduced caudate putamen and corpus callosum measurements) in Sheets (2001). There is a lack of data to suggest whether the effects seen in either study are the result of a single or multiple exposures. The draft RCD however interprets this uncertainty differently for each study. The POD derived from Sheets (2001) is assumed to have potentially occurred from a single exposure and is used to evaluate acute and short-term exposures, while the POD derived from Patel (2010) is assumed to have occurred from multiple exposures and is used to evaluate subchronic and chronic exposures. With no data to suggest otherwise and supported by

guidelines for interpretation and application of DNT study data (Makris et al., 1998), these DNT effects should be assumed to have the potential to occur from a single exposure event at any timepoint during the gestation and postnatal exposure period to achieve the most health protective approach and may be used for acute health assessment.

DPR Response: DPR considers certain developmental responses including changes in brain structural dimensions as potentially acute because they may result from a single or a few doses to the dams during a critical period of prenatal or postnatal organ development. On the other hand, neurobehavioral changes are more complex because they require involvement of many neural pathways, each becoming activated at different times during critical developmental windows. In the past, DPR has established critical acute PODs based on developmental neurobehavioral effects, but only when data were available to directly implicate acute or short-term exposures (e.g., see DPR's 2018 RCD on chlorpyrifos; DPR, 2018). However, no such data were found in studies with imidacloprid or other xenobiotics. Negative geotaxis in rats develops only during the second postnatal week. At PND 10 when altered negative geotaxis was first observed, the combined gestational and lactational exposure to imidacloprid was 31 days, which is a subchronic exposure duration. Moreover, no clearly acute effects were observed at imidacloprid doses that affected the negative geotaxis response. In fact, the lowest observed effect level (LOEL) for negative geotaxis was similar to the LOELs for other sensitive subchronic and chronic effects (e.g., immunotoxicity, thyroid toxicity, liver toxicity). Thus, DPR considered the altered negative geotaxis to have resulted from multiple doses of imidacloprid. For purposes of this assessment, the critical POD of 1.0 mg/kg/day was used to evaluate both subchronic and chronic risks to humans.

In conclusion, all critical PODs for imidacloprid were established from registrant-submitted studies based on neurodevelopmental effects, the acute POD of 5.5 mg/kg/day from Sheets, 2001 and the subchronic and chronic PODs from Patel, 2010. However, DPR was unable to establish a new acute POD from the Patel study because the weight of evidence was insufficient to categorize negative geotaxis as an acute effect. Numerous uncertainties are associated with the negative geotaxis test: 1) It is not included as part of US EPA's DNT test guidelines; 2) negative geotaxis has not been used in studies conducted for regulatory purposes on pesticides; and 3) the variations of the precise parameters used to define negative geotaxis differ across study and by investigator. Each of these issues is discussed further in the Risk Appraisal section of the final RCD.

OEHHA Comment, continued: Finally, studies in the open literature provide evidence of neurotoxic effects at doses below the current acute POD of 5.5 mg/kg-day. A 2015 study by Kara et al. showed developmental effects in postnatal rats following 90 days of imidacloprid exposure at 2 mg/kg-day starting at birth. Khalil et al. (2017) showed altered behavior, including decreased motor activity, in adult rats at imidacloprid doses as low as 0.5 mg/kg-day. DPR cited limitations of these studies including lack of information on purity of the test article and use of solvents that could confound the results. Although the identified open literature studies may not

have quantitative utility in the health assessment, they provide empirical evidence that the current acute POD derived from Sheets (2001) is not likely to be health protective against the most sensitive developmental and neurotoxic effects.

> **DPR Response:** As OEHHA indicated, both Kara et al. (2015) and Khalil et al. (2017) do not meet DPR's minimum data acceptance criteria (DPR, 2023) due to methodological reporting deficiencies which limited the reliability of their overall conclusions. As such, these papers were excluded from use in the quantitative, empirical or the overall weight of evidence in the imidacloprid health assessment. Furthermore, both studies reported findings that were subchronic in nature (90 days and 60 days, respectively), minimizing their relevance to the acute toxicity endpoint.

OEHHA Comment, continued: OEHHA also notes that the oral POD of 1.0 mg/kg-day is lower than the no-observed-adverse-effect level (NOAEL) calculated from the 5-day acute inhalation study by Pauluhn (1988). The NOAEL of 2.6 mg/kg-day is based on decreased body weight and induction of liver mixed-function oxidases. Deficiencies in study reporting prevent the use of this value to evaluate inhalation exposures. OEHHA agrees that the use of the oral POD to evaluate inhalation exposures (and also dermal exposures for which there are no available PODs) is both appropriate and health protective. Therefore, OEHHA recommends that a POD of 1.0 mg/kg-day based on altered negative geotaxis in male pup from Patel (2010) be used to assess all acute exposures to imidacloprid

> **DPR Response:** As noted in the draft RCD, the inhalation study by Pauluhn (1988) was inadequate for acute POD designation due to the lack of particle size analyses to inform on the fraction available for deposition or absorption.

2. Carcinogenicity

a. Genotoxicity

OEHHA Comment: OEHHA agrees that there is evidence of genotoxicity for imidacloprid in in vitro testing, but no clear evidence in vivo…However, there are some inconsistencies in the presentation of genotoxicity data that should be addressed. The Technical Summary and Risk Assessment sections state that imidacloprid is negative for genotoxicity in vivo, but positive in several in vitro tests. Table 13 in the Genotoxicity subsection of the Toxicology Profile, however, shows two studies with positive results in vivo. These studies are also listed in Appendix D for excluded studies. Additionally, there are in vitro studies in Table 13 that are also listed in the excluded studies in Appendix D. The text describes the database as comprising 18 studies with 52 assays. OEHHA recommends DPR review the draft RCD's sections on genotoxicity and related tables for accuracy and consistency in the presentation of data.

> **DPR Response:** Comments on this point are noted. Studies that did not meet DPR's criteria for data acceptance were removed from Table 13 in the main RCD and are now listed in Appendix D (Data Acceptance and Excluded Studies) of the final RCD. In addition, a new

in vitro study published in the open literature since DPR released the draft RCD for scientific review has now been added (Wei et al., 2024). The Technical Summary, Toxicology Profile, and Hazard Identification of the final RCD have all been edited to reflect these changes.

3. Extrapolation, Variability, and Uncertainty

a. Intraspecies Extrapolation

OEHHA Comment: DPR applied an uncertainty factor (UF) of 10 for intraspecies extrapolation (UFH), which comprises √10 for pharmacokinetics and √10 for pharmacodynamics. OEHHA recommends that DPR's default pharmacokinetic UF of √10 be increased to 10 to account for the wide variability of pharmacokinetics in the population and to protect sensitive populations. The total intraspecies UF would be 30.

DPR Response: A 10x default intraspecies UF consisting of a pharmacokinetic UF of 3 and a pharmacodynamic UF of 3 was applied to the acute, subchronic and chronic risk evaluations for imidacloprid. This is consistent with DPR's current practice (DPR, 2011) of applying a 10-fold total intraspecies uncertainty factor in all cases absent specific data to support a different or additional value. Following extensive review of imidacloprid specific data, DPR determined a UF of 10 is appropriate.

B. Exposure Assessment

1. Dietary and Drinking Water Exposure

a. Pesticide Residue Data

OEHHA Comment: OEHHA agrees overall with the approaches used to estimate the acute and chronic dietary exposures. When possible, OEHHA recommends using California-specific PDP residue and PCT databases. For example, there are 60 commodities in the PDP database with samples collected in California. These could be analyzed separately, to investigate whether California dietary exposure trends mirror those of the larger US sample, or display differences.

DPR Response: Foods sold in California are grown locally but also imported from other states and countries. Restricting the residue data to California-only foods may lead to potential underestimation of exposure because out-of-state or out-of-country samples may contain higher residue concentrations. The Tier 3 probabilistic dietary exposure analysis did not identify dietary risks. Therefore, further refinement was not necessary. For drinking water exposures, DPR focuses on relevant residues measured only in California waters because of the unique issues surrounding California hydrology, water distribution, and widespread agricultural practices not necessarily found in other parts of the country.

b. Surface Water Data

OEHHA Comment: The RCD used SURF samples collected in California from 2/12/2000 to 6/26/2019 and identified a maximum value of 9.14 ppb (Santa Barbara County, 9/17/14) for use in its drinking water assessment. The values used in the draft RCD are almost 5 years old. When OEHHA accessed the SURF database on April 2, 2024, and applied the same exclusion criteria as stated in the draft RCD, there was a significantly higher detection of 51.83 ppb in Oso Flaco Creek at Oso Flaco Lake Rd, San Luis Obispo County (5/12/20).

DPR Response: Thank you for identifying this monitored value. The anticipated imidacloprid residues in drinking water have been updated in the final EAD to reflect the highest value reported in the latest update to DPR's surface water database. This now includes the highest detection of 51.83 ppb (see Tables 26 and 29 in final RCD) which was recommended for use as the maximum concentration for calculating deterministic acute drinking water exposures in the final EAD. There was no change to the mean concentration of non-zero values for use in calculating chronic drinking water exposures and risk in the final RCD. Even with the incorporation of this highest detected residue, no risks were found to any of the evaluated subpopulations from either acute or chronic dietary and drinking water exposures.

c. Desnitro-imidacloprid Exposure

OEHHA Comment: The PDP database showed that desnitro-imidacloprid was detected in 27% of commodity samples analyzed between 2009 and 2021. This degradate was detected in three commodities: green beans, summer squash, and winter squash, with sample sizes of 854, 416, and 768, respectively (PDP database, accessed by OEHHA April 2, 2024). These sample sizes appear to meet the criterion of > 30 data points per commodity to conduct a distributional analysis (DPR, 2009).

Although DPR (2009) states that it is less desirable than NOAEL ratios, LD50s can be used to represent the quantitative difference between parent and degradate toxicity. In mice, the LD50 for desnitro-imidacloprid was lower than that for imidacloprid (16-24 mg/kg versus 35-49 mg/kg, respectively; Chao and Casida, 1997).

Furthermore, when metabolites have a similar mode of action, the adjusted metabolite should be added to the parent chemical residue to obtain total residue (DPR, 2009). Evidence presented in the RCD suggests that desnitro-imidacloprid and imidacloprid have a similar mode of action. However, DPR did not conduct separate dietary exposure assessments for these metabolites, citing that their detected levels were included in the total imidacloprid residue and were lower than the total imidacloprid levels. This appears to contradict DPR's 2009 guidance.

OEHHA recommends that DPR assess potential acute and chronic effects of dietary and drinking water exposure to desnitro-imidacloprid using degradant residue data and a relative comparison of toxicity of the desnitro-imidacloprid to its parent imidacloprid.

DPR Response: As recommended from OEHHA's review of the draft RCD, the dietary exposure assessment was expanded in the final RCD to include desnitro-imidacloprid. Following database searches for additional imidacloprid metabolites and degradates, both imidacloprid urea and olefinic imidacloprid were also included in this final assessment. Monitoring data were available for these three breakdown products of imidacloprid in 6 foods. No monitoring data were available for any other imidacloprid metabolite or degradate, and hence were not included in the final analysis. Imidacloprid urea, olefinic imidacloprid and desnitro-imidacloprid were monitored by PDP from 2008 to 2022 on 6 foods (winter squash, summer squash, green beans, pears, baby food-peaches, and mustard greens). The detection rate was about 1% for imidacloprid-urea and imidacloprid-olefin. While the detection rate for imidacloprid-desnitro was higher (27%), it was tested on only 3 foods.

DPR discussed the toxicity database for the imidacloprid metabolites and degradates in the draft RCD. There were no toxicity data in mammals for imidacloprid urea and olefinic imidacloprid. Similarly, there were no toxicity data for imidacloprid-desnitro except for a published intraperitoneal study in mice that reported lower LD50 values compared to the parent imidacloprid. This report did not provide sufficient information to establish the toxicity potency for this degradate relative to the parent. DPR thus considered all three compounds to have equivalent toxicity to imidacloprid for the dietary analysis. As such, concentrations of the metabolites/degradate were converted to imidacloprid equivalents, which were then added to the parent (if it was also detected in the sample) to derive a total imidacloprid residue for calculating the dietary exposure. Overall, the inclusion of the metabolites/degradate did not change the conclusions of the draft dietary exposure and risk because none of the 6 foods monitored for their residues was found to contribute to the high-end exposure. However, the dietary exposure could be impacted if residues of these compounds were available for foods like hops, corn syrup, grapes and water, which exhibited the highest contributions the dietary exposure. The residue data and the results from the dietary risk analysis are detailed in the final RCD.

2. Exposure Estimates for Non-agricultural Professional Handlers

a. Absorbed daily doses

OEHHA Comment: Estimated exposures for three handler scenarios could not be replicated using the cited methods and assumptions (Table 9). For handgun sprayer applications of flowable concentrate to ornamentals, OEHHA estimates for short-term (STADD), seasonal, annual and lifetime absorbed daily doses were 3-fold higher than corresponding EAD estimates. This discrepancy might be due to the EAD's use of a Maximum Application Rate of 0.1 lbs/100

gallons instead of the 0.3 lbs./100 gallon cited in Tables 7 & 9. For low-pressure handwand applications of aqueous concentrates to turf, the OEHHA STADD estimate for mixers/loaders/applicators was more than 12% lower than the reported EAD estimate. For aerial applications of soluble powders to turf, the OEHHA STADD estimate for applicators was approximately 10% higher than the EAD estimate. OEHHA could not identify a reason for the differences. For all scenarios, OEHHA estimates were based on the referenced Pesticide Handler Exposure Database-derived exposure rates for dermal (non-hand), hand (with gloves) and inhalation (DPR, 2007). OEHHA recommends that DPR review its calculations and revise the absorbed daily dose estimates for these 3 scenarios.

DPR Response: The discrepancy for the handgun sprayer was due to a typographical error in Tables 7 and 9. Specifically, the maximum application rate of 0.3 lbs./100 gallons was listed instead of the 0.1 lbs./100 gallons that was used in the exposure calculation which reflects the highest label rate. This has been corrected in the final EAD. Similarly, for the low-pressure handwand applications of aqueous concentrates to turf and aerial applications of soluble powders to turf, all input parameters for calculating the exposures were doublechecked for accuracy and are correct in the final EAD.

b. Personal Protective Equipment

OEHHA Comment: For the aerial applicators for the same turf scenario as described above, footnote "f" in Table 7 states that "the pilot is not required to wear gloves in a closed cockpit." However, this assumption does not seem to apply to the cited exposure scenario entitled, "Scenario 17: Aerial Applicator, Liquids, Open Cockpit" (DPR, 2007).

DPR Response: Footnote f, concerning 'the pilot is not required to wear gloves in a closed cockpit,' has been deleted because it was not used in evaluating exposure from scenario 17, as described in the comment.

3. Exposure Estimates for Non-agricultural Reentry Workers

a. Transfer factor

OEHHA Comment: OEHHA was unable to verify the transfer factor (TF) of 500 cm^2/hour used for the "Turf – Mowing, tractor or push" scenario (Table 10). OEHHA could not identify a value for this activity in the cited reference (US EPA, 2017a). OEHHA found another available source (US EPA, 2012) which recommended point estimates for use in post-application dermal exposure assessment of 5,500 cm^2/hour. DPR explained to OEHHA that the mower TF was derived from a turf maintenance study (TF=3,700 cm^2 /hour) that used samples from inner dosimeters, head/neck and hands (Klonne and Bruce, 2006). In the EAD, it was determined that the mowers' TF could be derived by multiplying the maintenance TF with the ratio of the mowers exposed surface area/total surface area. Thus, the mowers' TF = (2,341/17,213) × 3,700 cm2 /hour = 503 cm^2/hour. Representative adult surface areas for head, neck and hands were

derived by averaging male and female 50th percentile values (US EPA, 1997). OEHHA recommends that the assumptions and adjustment method be documented in the EAD (e.g., table footnotes) or that DPR consider an alternative TF source.

DPR Response: Additional explanation has been added to footnote b in Table 10 in the final EAD to elaborate on the differences between US EPA's and DPR's derivation and use of the transfer factor for the "Turf – Mowing, tractor or push" scenario. As described in our response to OEHHA's Summary Comment C.4. above, DPR derived a mowing-specific TF by scaling the US EPA TF of 3700 cm^2/hr by the ratio of exposed surfaces (head, neck and hands) to the total body surface area. This scaling allows for consideration of exposed body surface areas such as the head, neck, and hands, given that unlike other activities listed in Table 10, mowing does not involve direct contact with treated surfaces.

b. Turf transferrable residues

OEHHA Comment: OEHHA reviewed the cited reference (Kroiski, 2016) but was unable to replicate the turf transferrable residues (TTR) value of 0.675 µg/cm^2 used for turf reentry scenarios (Table 10). Per discussions with DPR, the TTR value of 0.675 µg/cm^2 in Table 10 was a typographical error and should have been revised to 0.525 µg/cm^2 throughout the EAD. Analyte recovery in Kroiski was > 90% and, to be consistent with DPR policy, the study value was not corrected for recovery. However, it was adjusted to account for the higher study application rate. OEHHA recommends revision of the TTR, Daily Exposure and STADD values to reflect this information. OEHHA also recommends that DPR revise footnote "f" of Table 10 to include the related information found in Table 6, footnote "c." Two studies with California-specific data, Kroiski (2016) and Veal (2020), were characterized by high sample recoveries and compliance with FIFRA (40 CFR 160) Good Laboratory Practice Standards, however the R-squared values were not mentioned. OEHHA suggests that Table 6 include R-squared values for these two studies. In Table 10, the fifth column heading is "DFR^c (µg/cm^2)." However, this heading applies to both TTR and dislodgeable foliar residue (DFR) data as the first two rows include turf-related assumptions and calculated values. OEHHA suggests that this column heading be revised for clarity.

DPR Response: A typographical error in Table 10 has been corrected in the final EAD. Additionally, the column title of DFR has been modified to TTR/DFR to reflect that the value within the column is either DFR or TTR. A footnote has been added to Table 6 to indicate that no adjustment was made to the measured TTR value of 0.656 µg/cm^2 due to high field recovery (i.e., >90%). The respective R-squared values of the studies by Kroiski (2016) and Veal (2020) have also been added to Table 6 in the final EAD.

c. Pesticide use summary

OEHHA Comment: Table 9 footnote "f" mentions the high-use season was based on the Pesticide Use Report (PUR) data for Fresno County in 2017–2021 that is summarized in Figure

4. Since Table 9 is intended to assess exposure for non-agricultural professional handlers, Table 8 and Figure 4 should indicate if they represent PUR data summaries for only non-agricultural imidacloprid use or for all uses. OEHHA suggests the supporting text be revised for clarity.

DPR Response: Text has been added to the section "A. Professional Handlers" in the final EAD to clarify how PUR data was used to estimate seasonal exposure of non-agricultural professional handlers. Specifically, the final EAD now states,

"It is noteworthy that PUR exempts reporting requirements for some non-agricultural uses (Yanga and Steinmann, 2018). Hence, if based solely on non-agricultural uses, the high-use seasons would likely be underestimated. Accordingly, for this assessment, the entire Fresno County PUR dataset was conservatively used to estimate the use season. Figure 4 summarizes aerial and ground applications of imidacloprid in Fresno County by month and percent of annual use calculated from PUR data."

4. Exposure Estimates for Residential Handlers and Home Users

OEHHA Comment: OEHHA was unable to verify exposure estimates for two scenarios. For applications using a push-type/rotary spreader (no glove) for granule products, the EAD referenced a 95th percentile exposure rate of 16,920 µg/lb AI for loader/applicators (Table 11). In contrast, US EPA (US EPA, 2012, page C-4) recommends a dermal unit exposure of 1,900 µg/lb. AI for the 95th percentile statistic. It is not clear why the EAD value is 8.9-fold higher. OEHHA also notes that the inhalation exposure rate differs between the EAD and the referenced US EPA (2012) value by 2.4-fold.

DPR Response: The short-term dermal and inhalation exposure values associated with the push-type/rotary spreader (no glove) are correct in Table 11. However, the draft EAD contained typographical errors in the corresponding 95th percentile exposure rates. Accordingly, Table 11 in the final EAD has been revised to reflect the correct 95th percentile dermal exposure rate (i.e., 1900 µg/lbs AI) and inhalation rate (i.e., 48.9 µg/lbs AI).

OEHHA Comment, continued: For applications using water-soluble packet products to treat construction or wood, OEHHA used the EAD inputs for application rate, application units/day and unit exposure for applicators. However, OEHHA calculated a dermal STADD 15% lower than the reported EAD value.

DPR Response: The short-term dermal and inhalation exposure values associated with the water-soluble packet products to treat construction or wood are correct in Table 11. However, the draft EAD contained a typographical error in the application rate. Accordingly, Table 11 in the final EAD has been revised to reflect the correct application rate (i.e., 0.012 lbs/gal).

5. Exposure Estimates for Pet Collar Handlers and Pet Collar Composition

OEHHA Comment: In the draft human health risk assessment for registration review of imidacloprid (US EPA, 2017), US EPA noted uncertainty over the solid or liquid composition of pet collar products as it significantly affects the estimated amount of imidacloprid exposure of pet handlers. A 50:50 ratio was assumed in the EAD. OEHHA recommends that the rationale for the 50%/50% (liquid/solid) composition assumption be included in the EAD to increase transparency. As noted in the US EPA (2017) and other recent documents, it is unclear how best to estimate pet collar composition and exposure. OEHHA also recommends that the pet handler scenarios be presented in a separate table to simplify both tables and improve overall clarity.

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 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; USEPA, 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. To improve the readability, Table 11 has been split into Table 11a and Table11b, where the latter describes pet handler exposure to imidacloprid.

6. Post-application Exposure of Residents and Home Users

OEHHA Comment: For incidental ingestion exposure to toddlers from treated turf (Table 17), the EAD estimated both hand-to-mouth and direct turf mouthing routes. OEHHA is concerned that daily exposure and STADD values could only be roughly approximated using the referenced default assumptions, EAD text and footnotes. Usually, daily exposure is adjusted with a default body weight to calculate STADD, however the reported STADD values are consistent with a non-standard 16.7 kg body weight adjustment. Footnotes “e” and “j” appear to be unnecessary for these calculations. Footnote “p” references an unexplained conversion factor. OEHHA recommends that the table be reviewed and revised for clarity.

DPR Response: The concerns raised by OEHHA on the EAD estimated both hand-to-mouth and direct turf mouthing routes are noted. However, in the absence of experimental data, it is a general practice to use default assumptions for deriving exposure estimates based on established DPR policy, which in this case, is the procedures described by US EPA (2012). Regarding the comment on non-standard 16.7 kg body weight adjustment, the draft EAD contained typographical errors for Exp (µg) and HR (µg/cm^2) used to calculate hand-to-mouth exposures in Table 17. Using the corrected parameters, the daily exposure (µg/day) is 791.2 and the STADD value is 60.9 using the body weight of 13 kg. The 13 kg body weight is the default body weight of 1–2 years old male/female listed in the DPR policy (Andrews and Patterson, 2000). Similarly, the draft EAD contained a typographical error for daily exposure (µg/day) for non-dietary grass ingestion; however, all input parameters used in the exposure estimate are correct. Using the corrected daily and body

weight of 13 kg, the STADD value is 1.85 as appeared in Table 17. For footnote "p," the exposure equations are obtained directly from US EPA (2012) and US EPA reference has been added in the final EAD.

OEHHA Comment, continued: For the hard surfaces exposure scenario - footnote "d" in Table 18 defines the deposited residue (DepR) for hard surfaces, 4.5 μg/cm^2, as a default value from US EPA (2012). This value corresponds to the recommended default residue value for "Perimeter/Spot/Bedbug (Coarse) treatment" (US EPA, 2012, Appendix D, page D-42). OEHHA recommends that this footnote also include the referenced treatment "Perimeter/Spot/Bedbug (Coarse) treatment" to improve transparency.

DPR Response: Footnote "d" has been expanded to describe the source of deposited residue (DepR) for hard surfaces.

OEHHA Comment, continued: For the Hand-to-Mouth (HtM) carpet exposure scenario - OEHHA is concerned that two EAD inputs (exposure time, surface area of one hand) in Table 18 differ significantly from the default values in the cited source (US EPA, 2012). The EAD mentions using a hand surface area (HSA) of 1–3 fingers, but the cited reference (US EPA, 2012) uses a default value of 150 cm^2 for one hand or approximately 30 cm^2 per finger. OEHHA is also concerned that the EAD applies a 1.5-hour exposure duration, citing an older and difficult-to-access document (US EPA, 2001) instead of the 4-hour exposure duration value from a more recent document (US EPA, 2012). OEHHA recommends that DPR discuss the rationale for these choices.

DPR Response: The STADD value of hand-to-mouth (HtM) carpet exposure scenario in table 18 is correct. However, typographical errors were introduced into two parameters used in the exposure calculation: exposure duration of 1.5 hours instead of 4 hours and hand surface area (HAS) of 20 instead of 150. Also, the reference of exposure duration in footnote "b" has been updated to USEPA (2012).

7. <u>Estimated adult and child dermal exposures to imidacloprid residues from spot-on treated pets</u>

OEHHA Comment: For estimated incidental oral exposure in children (aged 1–2 years) from imidacloprid residues from treated pets (Table 21), OEHHA has concerns similar to those previously stated for the HtM carpet scenario. The HSA value of 20 cm^2 for 1-3 fingers differs significantly from the recommended value of 150 cm^2/hand (US EPA, 2012). Consequently, related values such as hand residue loading, exposure and STADD for spot-on products could be approximated but not fully replicated. Lastly, for the HtM spot-on scenario, the reported STADD value is 2.67-fold less than would be predicted for a 13 kg body weight. OEHHA recommends that the table be reviewed for mathematical accuracy. OEHHA also recommends that any

unstated surface area-related assumptions or adjustments be noted in the footnotes or EAD text for clarity and transparency.

DPR Response: The STADD values of hand-to-mouth (spot-on) and hand-to-mouth (collar) in Table 21 are correct. However, the draft EAD contained typographical errors for hand surface area (HAS) (20 instead of 150) and hand residue loading (HR) (0.07 instead of 0.03). Using the corrected values, the daily exposure was revised to 1.95 µg/day and the revised STADD value, after dividing the daily exposure by body weight of 13 kg, is 0.15 µg/kg/day, as appears in Table 21 of the final EAD. Also, the reference of exposure duration in footnote "b" has been updated to US EPA (2012). Similarly, hand surface area (HAS) of 20 instead of 150 was listed for the hand-to-mouth (collar). This has also been corrected in the final EAD.

IV. RESPONSES TO CHARGE STATEMENTS

Because of the significant overlap in detailed responses and response to Charge Questions, only comment(s) requiring additional clarification from DPR, or that were considered in the finalization of the imidacloprid RCD or EAD, are discussed here.

DPR Charge Question: MOEs calculated for short-term exposures to home users were lower than the risk target of 100 for some scenarios, thus indicating a risk to human health from the use of some commercially available products containing imidacloprid.

OEHHA Comment: OEHHA agrees that there is risk from the use of some available home use pet products. It is concerning that all acute and subchronic exposure scenarios for adults applying imidacloprid-containing pet collars, three dermal and five combined dermal and oral post pet-product application exposure scenarios for children aged 1–2 years are below the DPR target MOE of 100 and would be below OEHHA's recommended MOE of 300.

Additionally, acute dermal exposure scenarios for children aged 3–8 years, acute incidental oral scenarios for children aged 1–2 years, and acute combined dermal and oral exposure scenarios for post-application exposure to treated turf are below the DPR target MOE of 100. All scenarios for post-application exposure to treated turf for individuals aged 1–18 years would be below the OEHHA suggested target MOE of 300.

DPR Response: As noted by OEHHA, this significantly affects the estimated amount of imidacloprid exposure of pet handlers. In response to comments and data received by US EPA and the imidacloprid registrant Elanco, Inc., DPR revised the exposure estimates involving pet collar scenarios. The revised exposure estimates are found in the final EAD. Corresponding revisions to the risk estimates for these scenarios, including for adult handlers/users and adult and child residents in post-application scenarios, have been incorporated into the final RCD.

Based on the new exposure values, all acute and subchronic dermal MOEs for adults and the dermal, oral or combined MOEs for children for the scenarios with pet products listed above are now greater than 900, thus indicating no risks to human health.

As discussed above, the DAF was updated based on submitted data. This resulted in changes to the post-application exposures for children from treated turf. All updated MOEs are greater than the DPR target of 100 except for the oral exposure to children aged 1–2 that remain a risk. Refer to Table 33 on the final RCD for the updated MOEs.

V. OTHER COMMENTS

DPR is grateful to OEHHA for its detailed review. Content suggestions, typographical errors, and suggestions for improved consistency and readability have been noted and incorporated as appropriate and according to DPR standards. Responses to specific comments are noted below.

OEHHA Comment: Page 49 of the draft RCD (Acute Toxicity Subsection of Toxicology Profile): In Table 8, there is a footnote that states the adjustments for respirable particles for inhalation studies. For the 4-hour dust inhalation study (Pauluhn, 1988), the text states the dose is adjusted by 11%, however that table indicates the dose is adjusted by 54, 57, and 18%.
Page 65 of the draft RCD (Genotoxicity subsection of Toxicology Profile): In Table 13, the last row mistakenly has Watanabe (1990) reported as being positive instead of negative for genotoxicity.

DPR Response: Comments on this point are noted. Formulas at the foot of the table entitled Summary of NOELs and LOELs Derived from Acute Exposure Studies of Imidacloprid (formerly Table 8, now Table 7) were added for all three acute inhalation studies and their correctness was confirmed. The result for Watanabe (1990) was confirmed as "negative" and revised.

OEHHA Comment: Page 142 of the draft RCD (Toxicity of Imidacloprid Metabolites and Degradates section of Uncertainties Associated with Imidacloprid Toxicity and Critical Points of Departure): There is no citation provided for the published intraperitoneal study in mice. Presumably this is a reference to Chao and Casida (1997), whose LD50 values in mice were cited in the previous imidacloprid RCD (DPR, 2006). However, the 2006 RCD incorrectly reported these values: the range for imidacloprid should have been 35–49 mg/kg, and the range for desnitro-imidacloprid should have been 16-24 mg/kg (Chao and Casida, 1997).

DPR Response: Comments on this point are noted. Chao and Casida (1997) was the correct source for the statement regarding the compared LD50 values on page 142; the citation was added to the RCD. The 2006 DPR RCD did report incorrect LD50 ranges for imidacloprid and desnitro-imidacloprid.

OEHHA Comment: Page D-22 of the draft RCD Appendices (Appendix D): In Table D.6., the in vivo results of Demsia et al. (2007) are grouped with in vitro entries.

> **DPR Response**: Comments on this point are noted. Demsia et al. (2007) reported both in vitro and in vivo studies. One occurrence of the in vivo study was found to be incorrectly grouped and was removed.

OEHHA Comment: The design of some tables is very complicated with many scenarios and footnotes. OEHHA suggests that the "Pets (dogs or cats)" section of Table 11 become a separate table as the scenarios seem quite different. The order of scenarios changes from table to table (Tables 7 and 9), which makes it difficult to match up the relevant assumptions, data, and estimates.

> **DPR Response:** Table 11 has been split into Table 11a and Table11b, where the latter describes pet handler exposure to imidacloprid. Regarding the order of scenarios in Tables 7 and 9, the grouping in Table 7 is based on "M/L", "M/L/A," "A', and "F" for identifying the exposure related work activities. For Table 9, the grouping is based on the application methods: aerial versus ground for highlighting the higher exposure associated with aerial than ground applications.

VI. REFERENCES

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