


Pesticide Exposure and Risk Assessment Evaluation

Document Review

Department of Pesticide Regulation's Draft Risk Characterization of Non-Agricultural and Residential Uses of Imidacloprid

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OEHHA
SCIENCE FOR A HEALTHY CALIFORNIA

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PREFACE

Under the authority of California Food and Agricultural Code Section 11454.1, the Office of Environmental Health Hazard Assessment (OEHHA) conducts scientific peer review of human health risk assessments prepared by the Department of Pesticide Regulation (DPR). DPR reports the risk assessment in two documents:

- The Risk Characterization Document (RCD), which summarizes the toxicology database of the chemical; discusses hazard identification and dose-response analyses; assesses dietary exposure, when appropriate; and characterizes the risk associated with the various exposure scenarios (dietary, occupational, residential, and aggregate exposures).
- The Human Exposure Assessment Document (EAD), which describes the relevant exposure scenarios and estimates exposure levels of workers and residents.

This report is a review of the draft RCD and draft EAD for non-agricultural and residential uses of the pesticide imidacloprid provided by DPR (dated and received March 07, 2024).

This peer review report has four parts:

I. Summary of Review
II. Detailed Comments
III. Responses to Charge Statements
IV. Other Comments

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I. SUMMARY OF REVIEW

This report presents the Office of Environmental Health Hazard Assessment (OEHHA) review of the draft Risk Characterization Document (RCD) for imidacloprid prepared by the Department of Pesticide Regulation (DPR). Imidacloprid is a systemic and contact neonicotinoid insecticide that is registered to control pests on agricultural and nursery crops, residential and structural pests, and parasites on companion animals. The draft RCD characterizes human health risks associated with non-agricultural exposures to imidacloprid from its use by professional handlers in landscape, residential and recreational settings, from consumer products including pet products, post-application risks to non-applicators, and dietary and aggregate exposures. Risks were assessed for acute, subchronic, and chronic exposures to workers, and acute and subchronic exposures to adult and child residents following use of flea and tick products and applications on turf. The draft Exposure Assessment Document (EAD) describes the exposure scenarios evaluated and estimates exposure levels of non-agricultural workers and residents.

OEHHA's principal comments are summarized here in Section I; they focus on issues that are likely to impact the key findings and conclusions of the assessment. Detailed comments are provided in Section II. Responses to DPR's charge statements (descriptions of scientific assumptions, findings and conclusions to be addressed by peer reviewers) are provided in Section III, and minor comments are provided in Section IV.

A. Toxicity Evaluation

1. The toxicity database is adequately described in the draft RCD. The limitations of the available dermal and inhalation studies are well described and the rationale for using oral points of departure (PODs) to assess these pathways is justified.
2. The draft RCD appropriately addresses the limitations in the availability of toxicity data for the metabolites of imidacloprid. OEHHA agrees that this data gap adds uncertainty to the assessment.
3. DPR's calculated dermal absorption factor (DAF) of 17% is an unnecessarily conservative estimate. A DAF of 5% should be adequately health protective and supported by guidance on the interpretation of experimental data for dermal absorption (OECD, 2022).
4. OEHHA recommends using the benchmark dose (BMD) modeled value of 1.0 mg/kg-day based on developmental neurotoxicity (DNT), demonstrated by altered negative geotaxis in male pups on postnatal day (PND) 10, from Patel (2010) as the acute oral POD. This POD is more health protective and was derived with less uncertainty than the POD from the Sheets (2001) study, which was also based on developmental neurotoxicity.

5. OEHHA agrees with the critical subchronic oral POD of 1.0 mg/kg-day based on altered negative geotaxis in rat pups (Patel, 2010). This value is similar to or lower than other subchronic values in the database and will be protective of those observed effects.
6. OEHHA agrees with the critical chronic oral POD of 1.0 mg/kg-day based on altered negative geotaxis in rat pups (Patel, 2010). Based on the data available, the subchronic POD should also be protective of chronic exposures to imidacloprid.
7. OEHHA agrees that there is insufficient data to characterize or evaluate imidacloprid as a carcinogen.

B. Risk Characterization

1. DPR applied an uncertainty factor (UF) of 10 for intraspecies extrapolation (UF_H), 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.
2. The Margin of Exposure (MOE) approach was used to evaluate non-cancer hazards. The draft RCD characterized whether an exposure is likely to cause adverse health effects using a target MOE of 100 for all age groups. OEHHA recommends a target MOE of 300 to take into account the recommended higher intraspecies UF.

C. Exposure Assessment

1. Overall, the approaches taken by DPR appeared to be sound and followed standard exposure assessment methods. The assessment examined key exposure scenarios, routes of exposures, and appropriate endpoints (daily dose metrics).
2. OEHHA found parts of the EAD difficult to follow and suggests revising some sections and tables to clarify the assumptions and inputs. Also, several calculations were difficult to replicate. For example, the hand-to-mouth and similar estimates could not be replicated using the provided inputs and formulas. Some key details appeared to be lacking from tables and some referenced documents were not readily available (e.g., US EPA, 2001) or have been replaced by newer resources (US EPA, 2012).
3. There are instances in the EAD where the numbers and units provided are not reflected in the references cited. OEHHA suggests DPR verify the accuracy of the information provided to support its estimations.

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.
5. OEHHA agrees overall with the approaches used to estimate the acute and chronic dietary exposures. When possible, OEHHA recommends using California-specific Pesticide Data Program (PDP) residue data and percent crop treated (PCT) data.
6. OEHHA agrees with using the maximum imidacloprid residue detection in surface water to assess acute drinking water exposure. The RCD and EAD identified 9.14 parts per billion (ppb) as the maximum imidacloprid concentration in surface water and used this value to assess drinking water exposures. However, there is a more recent, higher value (51.83 ppb) in DPR’s surface water database. OEHHA recommends updating the maximum value used in the assessment.
7. OEHHA recommends that drinking water and dietary exposure to imidacloprid’s major environmental degradation product, desnitro-imidacloprid, be examined in greater depth. Due to its higher affinity for mammalian nicotinic acetylcholine receptors (nAChR) and toxicological significance, potential acute and chronic dietary exposure effects of this degradate should be assessed, at least qualitatively.

II. DETAILED COMMENTS

OEHHA's comments on the draft RCD for imidacloprid are grouped by A) Toxicity Evaluation and Risk Assessment and B) Exposure Assessment.

A. Toxicity Evaluation and Risk Assessment

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

a. Pharmacokinetics

The absorption, distribution, metabolism, and excretion of imidacloprid are adequately addressed in the draft RCD. Studies in rats show that oral absorption is over 90% with urine as the main route of elimination. Based on these data, OEHHA agrees with the assumption of 100% oral absorption. Following absorption, imidacloprid is rapidly distributed and metabolized within the body. There is little to no toxicity data available for many of the known imidacloprid metabolites including 6-chloronicotinic acid and its glycine conjugate, 5-hydroxy-imidacloprid, olefinic imidacloprid, a glycine conjugate of 6-methylmercaptonicotinc acid, and desnitro-imidacloprid. Desnitro-imidacloprid is the major degradation product of imidacloprid within the environment. It is a minor metabolite in humans (less than 3% of identified metabolites in rats and incubation studies with human microsomal enzymes), has no toxicity data available, and is considered to be the active human metabolite. The limited data available regarding its mechanism of action suggests that this moiety may be more toxic to humans due to nicotine-like behavior, an increased affinity for binding to human nicotinic acetylcholine receptors, and signaling activation at concentration levels 100-fold lower than imidacloprid. With no toxicity data available, OEHHA agrees this data gap adds uncertainty to the assessment.

There are no studies available on inhalation absorption, so a default absorption rate of 100% was used. OEHHA agrees with this determination.

b. Dermal Absorption Factor

A registrant-submitted in vivo dermal absorption study applying the Gaucho FS 350 formulation of imidacloprid (Odin-Feurtet, 2009) was used to estimate the dermal absorption factor (DAF) in the draft RCD. Male rats (4 rats/dose/timepoint) were exposed to a single, 8-hour dermal application of a low dose (0.5 grams per liter acetonitrile or g/L), intermediate dose (70 g/L), or neat product (350 g/L) of [^{14}C]-radiolabeled imidacloprid (>98% purity). Samples including urine, feces, cage wash, skin swabs, tape strips, cardiac blood, carcass, dressings and fur were collected at 8, 24, 72, and 168 hours after the start of exposure and analyzed for radioactivity.

The DAF is represented as the sum of the amounts of imidacloprid in collected samples considered to be directly absorbed or absorbable. These amounts include the total

percent of applied imidacloprid detected in excreta (urine, feces, and cage wash), in the carcass and cardiac blood, and removed from treated and surrounding skin at the application site. At the application site, imidacloprid amounts were calculated in the treated and surrounding skin after tape stripping was completed and represent imidacloprid that has penetrated the stratum corneum (the outermost 15-20 cell layers of the skin) and is available to be absorbed. Tape stripping is a commonly used procedure which sequentially removes the layers of the stratum corneum to determine how well a chemical penetrates and moves through the stratum corneum, providing information on whether the chemical amount in the skin is absorbable.

DPR calculated a DAF of 17% from this dermal study, combining the amount of imidacloprid that was directly absorbed, the amount present at the application site, and the amount of pesticide bound in the stratum corneum. Inclusion of the amount of pesticide bound in the stratum corneum as absorbable is in contrast with the study authors' determination that this amount is non-absorbable and the OECD Guidance Notes for the Estimation of Dermal Absorption Values (OECD, 2022). The study authors reported that the amount of pesticide bound in the stratum corneum was stable across all timepoints (8, 24, 72 and 168 hours) within each dose group (low, intermediate, and neat product) and considered this amount to be non-absorbed. The OECD guidance advises that in a study with sufficient sampling timepoints after dermal exposure has ended, chemical amounts remaining in the stratum corneum can be excluded from the DAF calculation if completion of absorption can be demonstrated. 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. OEHHA analyzed the available data and by 72 hours in the 168-hour study duration, over 85% of the total imidacloprid absorbed was detected in urine, feces, cage wash, non-treated skin (defined in the study as skin that was clearly separated from the application site), cardiac blood, and carcass for each dose group (Appendix I, Table A1). This suggests that absorption of the amount of imidacloprid detected in the stratum corneum is expected to be low and the amount can be excluded from the total amount of absorbable imidacloprid.

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.

c. General Approaches

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.

d. Acute Toxicity

In rodents, changes in body weight, gait, and motility, labored breathing, and neurotoxic effects including tremors, behavioral changes, and motor and locomotor activity, were observed following acute exposures to imidacloprid. The PODs for these effects ranged from 1.0 to 50 mg/kg-day. The draft RCD selected an acute POD of 5.5 mg/kg-day based on reduced brain morphometric measurements and motor activity changes in female rat pups from a DNT study by Sheets (2001). This POD is an estimated-no-effect level (ENEL) based on the study's lowest-observed-adverse-effect level (LOAEL) of 54.7 mg/kg-day. In the study, brain measurements were made in the control and high dose groups only. Measurements for the low and mid dose groups could not be performed due to shrinkage associated with continued storage. When compared to historical control values, the mean study values were found to be within the historical ranges and the study authors postulated in a subsequent publication that changes in brain measurements of the caudate putamen were not treatment-related (Sheets, 2016). Thus, there is uncertainty associated with the LOAEL of 54.7 mg/kg-day.

In a second DNT study in the imidacloprid database (Patel, 2010), a POD of 1.0 mg/kg-day based on altered negative geotaxis was derived. The negative geotaxis reflex is a measurement of development and neuromotor abilities in young rodents, which develops by the second postnatal week in normal rat pups and is included in the OECD 2007 guidelines (Test No. 426) for the evaluation of the DNT of chemicals. This is the only study in the imidacloprid database that evaluated changes in this particular reflex following exposure. Although OEHHA was unable to find examples of negative geotaxis used in risk assessments of pesticides by public agencies, use of this endpoint in the toxicity evaluation of pesticides is supported by studies in the open literature of other neonicotinoids and other classes of pesticides (neonicotinoids: Haddad et al. (2023), Tanaka (2012a), Tanaka (2012b); organophosphates: Lan (2017), Cole et al. (2012),

Mustafa & Al-Baggou (2020), Dam et al. (2000), Acker et al. (2011); pyrethroids: Farag et al. (2006), Godinho et al. (2017)). These studies demonstrate a pattern of use for this assay in the evaluation of other pesticides which have been documented to produce neurotoxic and DNT effects. In addition to altered effects on rodent reflexes, effects on motor and locomotor activity were also observed in several of these studies, similar to those seen in both Patel (2010) on day PND 10 and Sheets (2001) on PND 17. Thus, the scientific literature supports negative geotaxis as an appropriate critical effect to assess the toxicity of imidacloprid.

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.

Second, the nature of the critical effects for both studies are not vastly different. In Sheets (2001), neurotoxic effects on brain morphometry and activity were observed on PND 11 and 17, respectively. In Patel (2010), neurotoxic effects on reflex development and activity were observed on PND 10 and 13, respectively. The NOAELs for these effects are 5.5 mg/kg-day (LOAEL-to-NOAEL extrapolation, 10 UF) in Sheets (2001) and 7.39 mg/kg-day (LOAEL = 17.56 mg/kg-day) for Patel (2010). The negative geotaxis data are amenable to BMD modeling and a benchmark response of 5% extra risk provides a $BMDL_{05}$ of 1.0 mg/kg-day, a value that is 5-fold lower than the ENEL value from Sheets (2001). Based on the similarity in the timeline of occurrence of critical effects, it is reasonable to expect that the lower POD will also be protective of effects on brain measurements.

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.

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.

e. Subchronic and Chronic Toxicity

The most sensitive effects in animal studies following subchronic exposure to imidacloprid included effects on body weight, trembling, liver toxicity, reduced delayed-type hypersensitivity, altered reflexes, and motor function deficits. Decreased body weight and liver toxicity, in addition to thyroid toxicity, were also observed following chronic exposure. The most sensitive subchronic and chronic PODs were similar and ranged from 0.9 to 1.9 mg/kg-day, all derived from BMD modeling as shown in the table below. The lowest POD of 0.9 mg/kg-day was based on reduced delayed-type hypersensitivity in mice (Badgujar et al., 2013). Uncertainties in the study design and response measurements provided a lack of support for this value to be used as the critical POD. An oral developmental toxicity study in rats (Patel, 2010) with the critical effect of altered negative geotaxis in male pups and a chronic oral study in rats (Eiben and Kaliner, 1991; Eiben, 1991) with the critical effect of increased incidence of mineralized particles in the thyroid provided the next lowest BMDL value of 1.0 mg/kg-day. The Patel (2010) DNT study value was selected as the critical subchronic POD that will be protective of other observed subchronic effects. OEHHA agrees with this determination as it is similar in magnitude to the lowest potential POD of 0.9 mg/kg-day from Badgujar et al. (2013) and there is more confidence in the Patel (2010) study results compared to Badgujar et al. (2013).

DPR also used the subchronic POD as the chronic POD based on the similarity in magnitude of POD values observed following chronic exposure. The chronic studies did not evaluate behavioral or functional endpoints; such endpoints are often only examined in DNT studies. Despite the shorter exposure durations used to conduct DNT studies, in circumstances where DNT effects are the most sensitive effects observed in a chemical's database, and because the effects result from exposure during a specific window of susceptibility (in utero and/or during lactation), these endpoints may be used

to evaluate chronic exposures (Makris et al. 2009). OEHHA agrees that the use of this critical POD is appropriate for assessing both subchronic and chronic exposures to imidacloprid.

Lowest Subchronic and Chronic Points of Departure for Imidacloprid

Species/Strain	Study Type and Exposure	Critical effect	POD	Reference
Rat, Wistar	Dietary, DNT, GD0-LD21	Altered negative geotaxis	$BMDL_{05}$=1.0 mg/kg-day	Patel, 2010
Mouse, BALB/c	Gavage, Immunotoxicity, 4 weeks	Decreased DTH response	$BMDL_{1SD}$=0.9 mg/kg-day	Badgujar et al., 2013
Rat, Wistar	Dietary, chronic/ oncogenicity, 104 weeks	Mineralized particles in the thyroid	$BMDL_{10}$=1.9 mg/kg-day[a]	Eiben and Kaliner, 1991; Eiben, 1991
Rat, Wistar	Inhalation, 4 weeks, 6 hours/day, 5 days/week	Elevated ALT in serum	$BMDL_{1SD}$=1.5 mg/kg-day	Pauluhn, 1989

[a] OEHHA calculated a $BMDL_{05}$=1.0 mg/kg-day

DNT, developmental neurotoxicity; POD, point of departure; GD, gestation day; LD, lactation day; SD, standard deviation; DTH, delayed-type hypersensitivity; ALT, alanine transaminase.

f. Reproductive and Developmental Toxicity

No reproductive effects were observed in the registrant-submitted two generation reproductive toxicity study in rats at imidacloprid doses of 5 to 121 mg/kg-day. However, several studies identified in the literature by OEHHA have shown reproductive effects in young and adult animals at doses similar to the proposed critical POD of 1 mg/kg-day. Bagri et al. (2015) reported sperm head abnormalities following a 14-day exposure of adult male rats to 5.5 mg/kg-day imidacloprid which resulted in increased fetal death 6 weeks post mating. Benchmark dose modeling of sperm head abnormalities at 14- and 21-days returned PODs (calculated with a benchmark response (BMR) of 1 standard deviation (SD), $BMDL_{1SD}$) of 0.6 and 0.7 mg/kg-day, respectively. Ninety-day exposure to low doses of imidacloprid were shown to have significant effects on sperm concentrations (Bal, 2012a; Zhao et al., 2021) at LOELs of 0.06 and 2 mg/kg-day. Juvenile rats were reported to have decreased testosterone levels and absolute epididymis weights at a dose of 0.5 mg/kg-day for 90 days. Abdel-Rahman Mohamed et al. (2017) exposed both juvenile and adult rats to a single dose of 1 mg/kg-day of imidacloprid. Results showed decreased relative seminal vesicle and testes weights, decreased sperm concentration and motility, and increased incidence of abnormal sperm. Three-month-old rats exposed to imidacloprid for 28 days had significantly decreased absolute testes weights at a dose of 2.2 mg/kg-day and DNA damage to

sperm cells at all doses of 0.06, 0.8 and 2.25 mg/kg-day (Lovakovic et al., 2021). The only study of reproductive toxicity judged acceptable by DPR during the Pesticide Contamination Prevention Act (PCPA) review proceedings (2022) was Bagri et al. (2015), but it was deemed unacceptable for the RCD based on reporting issues and inadequate test animal details. While there are limitations to the open literature studies, the observed reproductive effects at these low doses of imidacloprid are concerning and these effects should not discounted.

The database for developmental toxicity includes the following oral studies: developmental studies in the rat and rabbit, one each of acute and subchronic neurotoxicity studies in rats, and two DNT studies in rats. The results of these studies are presented in Tables 15 and 21 of the draft RCD.

In rats, observed effects in dams included decreased body weight and food consumption (Becker et al., 1992). Developmental effects on pups included increased incidences of wavy ribs and delayed ossification of sternebrae. Neurotoxicity effects observed included decreases in motor and locomotor activity (Sheets, 2001; Patel, 2010), reduced brain measurements (Sheets, 2001; Patel, 2010), and altered negative geotaxis (Patel, 2010). In rabbits, increased mortalities were seen in dams and developmental effects showed decreased fetal body weights and increased post-implantion loss (Becker and Biedermann, 1992). Potential PODs (including calculated BMDLs) for these observed effects ranged from 1.0 to 30 mg/kg-day.

DPR's selected oral PODs of 5.5 (Sheets, 2001) and 1.0 (Patel, 2010) mg/kg-day to evaluate acute and subchronic/chronic exposures, respectively, are based on DNT endpoints. OEHHA agrees that DNT effects are the most sensitive and appropriate endpoints to derive critical PODs for imidacloprid, however, OEHHA recommends that the Patel (2010) study be used to derive the acute POD. Patel (2010) has a similar study design as Sheets (2001) and observed sensitive effects at similar timepoints with a lower POD. In both studies, there are no data to determine whether the observed effects occurred from a single or multiple exposures, or whether the effects resulted from in utero exposure, lactational exposure, or both. Thus, for all exposure scenarios, the most health protective assumptions should be applied, and DNT effects could result from an acute exposure during a critical window of development. Additionally, as discussed in Section II.A.1c, open literature studies (even those of limited utility to derive a critical POD) provide evidence that suggests the acute POD proposed in the draft RCD is not likely to be health protective against all developmental and neurotoxic effects observed at lower doses of imidacloprid than used in the guideline toxicity studies. The POD derived from Patel (2010) is similar in magnitude to the NOAELs observed in those open literature studies where developmental and neurotoxic effects occurred and is also similar to NOAELs where reproductive effects occurred, as described above. The available evidence suggests the current subchronic and chronic POD of 1.0 mg/kg-day based on altered negative geotaxis will likely be protective of the sensitive acute effects of imidacloprid exposure, in addition to potential reproductive

effects among other subchronic and chronic effects discussed in Section II.A.1d, and should be applied as the critical POD for all exposure durations.

2. Carcinogenicity

a. Genotoxicity

Imidacloprid was positive in five out of fifteen studies (thirteen registrant submitted and two open literature) in its genotoxicity database. Positive assays include mutations in TK6 human lymphoblast cells, DNA damage in HepG2 human hepatoblastoma cells and TK6 human lymphoblast cells, and chromosomal damage in primary human lymphocyte cells and TK6 human lymphoblast cells. There are additional positive studies presented in Appendix D of the draft RCD. Though these studies showed positive results, some did not show a dose-related response or were positive at a single dose or concentration only, thus making interpretation of the results unclear. Nonetheless, they may provide some support for the results observed in the other positive studies. Therefore, 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.

b. Human and Experimental Animal Evidence of Oncogenicity

OEHHA agrees with DPR's conclusion to not analyze cancer risk, as there was insufficient evidence of tumors in the guideline rat (Eiben 1991; Eiben and Kaliner, 1991) and mouse (Watta-Gerbet 1991a and b) carcinogenicity studies. There is no human data on the oncogenicity of imidacloprid.

3. Extrapolation, Variability, and Uncertainty

a. Intraspecies Extrapolation

In the draft RCD, a default UF of 10 was applied to account for intraspecies variability within the human population (UF_H). This is generally subdivided into a factor of $\sqrt{10}$ for pharmacokinetics and $\sqrt{10}$ for pharmacodynamics. However, it appears that a default toxicokinetic value of $\sqrt{10}$ may not be adequate, particularly for sensitive subgroups

such as infants (OEHHA, 2008; Zeise et al., 2013). The scientific basis for this finding is detailed in OEHHA's peer reviewed *Air Toxics Hot Spots Risk Assessment Guidelines, Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (OEHHA, 2008). Based on analyses of human pharmacokinetic variability, OEHHA recommends increasing the traditional intraspecies pharmacokinetic UF of √10 to 10, resulting in a total UF_H of 30. This increase would account for the wide variability in pharmacokinetics in the population and be health protective of individuals who are more sensitive to toxic exposures due to life-stage, health or immune status, genetic and epigenetic variability, or individuals and communities disproportionately burdened by multiple sources of pollution.

b. Risk Characterization

The Margin of Exposure (MOE) approach was used to evaluate non-cancer hazards in the draft RCD. A target MOE of 100 was considered as health protective for all exposure groups and durations. This was based on 10-fold UF for interspecies extrapolation and 10-fold for intraspecies variability. OEHHA agrees that the default 10-fold UF for interspecies extrapolation is likely sufficient to protect human health when the point of departure is estimated from an animal study. However, as discussed in Section II.A.3a, OEHHA believes an increased intraspecies UF (from 10 to 30) is appropriate to adequately account for human pharmacokinetic variability. Thus, OEHHA recommends a target MOE of 300 for all age groups, occupational and non-occupational.

B. Exposure Assessment

1. Dietary and Drinking Water Exposure

a. Pesticide Residue Data

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.

b. Surface Water Data

OEHHA agrees with the EAD's rationale to exclude surface water sites considered as non-potable water sources and the RCD's use of the maximum detected value from DPR's Surface Water Database (SURF) to estimate acute exposure from drinking water. 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. However, 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).

As noted in the RCD, there have been “increased label-approved uses on food crops and increased detections in surface and groundwater since 2006.” This appears to be consistent with the higher maximum imidacloprid surface water detection in 2020 versus 2014. Considering that the RCD dietary analysis identified drinking water as “the main contributor to dietary exposure of infants, children, women of childbearing age and non-Hispanic-other subpopulations,” it is important that the most up-to-date values be used. OEHHA recommends that DPR update the drinking water analysis and include the more recent maximum detection value.

c. Desnitro-imidacloprid Exposure

With respect to both dietary and drinking water analysis, the RCD states that the imidacloprid degradate desnitro-imidacloprid was detected independently of imidacloprid in California surface water, and therefore would be particularly relevant for drinking water exposure. This degradate is the major environmental degradation product of imidacloprid. It is noted that this degradate has higher affinity for mammalian nAChRs than insect nAChRs, is considered the active metabolite in mammals, has similar potency to chronic nicotine treatment (and greater potency than imidacloprid) at upregulating nAChRs in mammalian brain, and was reported to have a lower median lethal dose (LD_{50}) than imidacloprid in mice. This information suggests, as stated in the RCD, that desnitro-imidacloprid is more toxic in mammals than the parent compound. However, the RCD did not follow up on these observations by conducting a separate assessment of this degradate.

DPR’s guidance document for dietary exposure assessment (DPR, 2009) states that when the parent chemical is converted to toxicologically significant environmental degradates, DPR will assess the exposures. With sufficient residue data, this document directs that degradates are to be included in the dietary exposure assessment for the parent chemical, even when toxicity data specific to the degradate are lacking. 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, LD_{50}s can be used to represent the quantitative difference between parent and degradate toxicity. In

mice, the LD_{50} 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 degradate residue data and a relative comparison of toxicity of the desnitro-imidacloprid to its parent imidacloprid.

2. Exposure Estimates for Non-agricultural Professional Handlers

a. Absorbed daily doses

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.

b. Personal Protective Equipment

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). OEHHA recommends that the Table 7 footnote be revised for clarity and to be consistent with the referenced exposure rate for aerial applicators (DPR, 2007).

3. Exposure Estimates for Non-agricultural Reentry Workers

a. Transfer factor

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 cm^2 /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.

b. Turf transferrable residues

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). Using the label maximum application rate of 0.4 lbs./acre (i.e., 20% less than the Kroiski study) shown in Table 2, OEHHA estimated a TTR of 0.553 µg/cm^2. 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."

The Eberhart and Ellisor (1994) and Welsh et al. (DPR, 2005) studies were not used to estimate TTR for a variety of reasons, including non-California location and high data variability as indicated by low R-squared values. 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/cm2)." 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.

c. Pesticide use summary

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.

4. Exposure Estimates for Residential Handlers and Home Users

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.

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.

OEHHA recommends that DPR review its calculations and revise the absorbed daily dose estimates for these 2 scenarios.

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

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.

6. Post-application Exposure of Residents and Home Users

For post-application turf exposures, DPR used a registrant study with exercising volunteers on a treated grass field (Eberhart and Ellisor, 1994) to estimate dermal and inhalation exposure from turf. OEHHA agrees with this approach.

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.

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.

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.

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

For estimated adult and child dermal exposures to imidacloprid residues from spot-on treated pets (Table 19), the column heading “Exposure (µg/day)” is incorrect as these are default body weights. However, the STADD values are accurate. OEHHA recommends the table be revised to include the dermal exposure values.

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.

III. RESPONSE TO CHARGE STATEMENTS

DPR asked OEHHA to address charge statements in its peer review of the draft RCD and EAD. The answers provided in this section are purposely brief with more in-depth discussion of these answers and OEHHA's other comments in Section II, Detailed Comments.

A. Toxicity and Hazard Identification

1) The acute oral point of departure of 5.5 mg/kg-day was based on developmental neurotoxic effects in rat pups.

As DPR states in the RCD, losses in brain structures can potentially result from a single exposure during development; this should also be true for negative geotaxis. Therefore, OEHHA recommends that the subchronic POD of 1 mg/kg-day based on significantly altered negative geotaxis in male rat pups on PND 10 (Patel, 2010) also be applied to acute exposure scenarios. There is greater uncertainty in the estimated-no-effect level (ENEL) derived from brain measurements from Sheets (2001) due to lack of measurements in the low- and mid-dose groups, whereas the effect on negative geotaxis (Patel, 2010) shows a dose-response, has an experimentally derived NOAEL, and is amenable to benchmark dose modeling. As both endpoints were measured in PND 10-11 rats, and both studies utilized similar gestational and lactational exposure parameters, the health protective approach is to assume that either alterations in brain structures or neurobehavioral effects could occur after a single exposure during a critical period of development in utero or during lactation. Thus, it is recommended that the endpoint occurring at the lower dose and with less uncertainty be used as the acute POD.

2) The subchronic oral point of departure of 1.0 mg/kg-day was based on developmental neurotoxic effects in rat pups.

As described in Section II.A.1d, OEHHA agrees that the selected POD value of 1.0 mg/kg-day based on developmental neurotoxic effects in male rat pups is appropriate and will be protective of the effects of subchronic exposure to imidacloprid. Additionally, limited evidence in the literature as discussed in Section II.A.1e indicates adverse reproductive organ and function effects in juvenile and adult rodents following exposure to imidacloprid at doses similar to the selected POD. Thus, OEHHA believes this POD will also be protective of those sensitive effects.

3) The subchronic oral point of departure of 1.0 mg/kg-day was also used as the critical chronic oral value.

OEHHA agrees with the use of the subchronic oral POD as the critical chronic oral POD as described in the draft RCD. The 1 mg/kg-day value is within the same magnitude as the lowest chronic POD calculated by DPR ($BMDL_{10}$ of 1.9 of mg/kg-day based on mineralized thyroid particles; Eiben and Kaliner, 1991). Using a benchmark response of

5%, OEHHA calculated a $BMDL_{05}$ of 0.9 mg/kg-day as the lowest potential chronic POD from the same endpoint. As described previously in Section II.A.1d, the POD selected in the draft RCD based on altered negative geotaxis should be protective of effects observed in the chronic toxicity studies.

4) **Points of departure from dermal and inhalation studies were not used to establish critical PODs.**

Acute and subchronic dermal and inhalation studies for imidacloprid are available, however, study deficiencies preclude their use to derive critical PODs. No chronic dermal or inhalation studies are available. OEHHA agrees that the application of oral PODs to estimate dermal and inhalation toxic effects is appropriate.

5) **This assessment did not include a cancer risk estimate for imidacloprid.**

Available animal data do not suggest that imidacloprid induces treatment-related tumor formation following long-term exposure. OEHHA agrees with DPR's decision not to perform a quantitative assessment of cancer risk to imidacloprid.

B. Exposure

1) **The exposure estimates relied on DPR's Pesticide Use Report (PUR) database.**

OEHHA acknowledges that imidacloprid exposure of certain professional applicators may be underestimated due to pesticide use reporting exemptions.

2) **Transferable turf residues (TTR) were used for estimating post-application exposure from turf.**

OEHHA concurs with DPR's use of the TTR derived from Kroiski (2016), once corrected (see Section II.B.3b), as a high-end estimate.

3) **DPR applied a seventeen percent (17%) dermal absorption rate in its exposure assessment.**

As discussed in Section II.A.1a, imidacloprid dermal absorption rates lower than those derived by DPR have recently been cited by other regulatory agencies (US EPA, 2019) and the calculated DAF of 17% may be unnecessarily conservative. OEHHA believes the amount of imidacloprid retained in the stratum corneum can be excluded from the total absorbed dose per OECD guidance on interpretation of experimental data from dermal absorption studies. A recalculated DAF of 5% would likely be sufficiently health protective.

4) **Imidacloprid concentrations in surface water were derived from DPR's Surface Water Database (SURF).**

OEHHA agrees with the use of DPR's SURF database to derive imidacloprid surface water concentrations. However, as described in Section II.B.1b, OEHHA recommends

that DPR use the more recently detected values from the SURF database, including the higher maximum value. Additionally, the EAD recommends “the mean concentration of the non-zero values (0.361 ppb) be used to calculate chronic exposure.” As drinking water levels are increasing over time, a mean concentration from more recent years would better approximate current levels in drinking water compared to averaging data from 2000 to 2019.

5) **Composition of active ingredients in impregnated pet collars.**

In its 2019 updated exposure assessment for imidacloprid, US EPA estimated exposure from liquid (99.71%) and dust (0.29%). In the EAD, the rationale for setting the composition as 50% liquid/50% solid is not clearly stated. OEHHA recommends stating the rationale for this composition.

C. Risk Characterization

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.**

OEHHA agrees with the use of 10-fold UF for interspecies extrapolation.

However, as described in Section II.A.3a, OEHHA recommends a combined intraspecies UF of 30 to account for wide variability in pharmacokinetics in the human population, especially due to susceptible life-stages, health, immune, and genetic factors, and disproportionate pollution burden.

2) **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 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.

3) **Dietary (food and drinking water) exposures did not make a substantial contribution to the overall risk when aggregated with occupational and non-occupational exposures.**

OEHHA agrees with the approach used for dietary analyses. As discussed in Section II.B.1c, OEHHA recommends that DPR discuss in more detail how the potentially increased toxicity of desnitro-imidacloprid might affect the estimated dietary risks, e.g., a relative comparison of toxicity of the desnitro-imidacloprid to imidacloprid. Additionally, OEHHA recommends using California-specific data, when available, to update the assessment before finalizing the RCD and including the most recent residue and water monitoring data available.

IV. OTHER COMMENTS

A. Toxicity Evaluation and Risk Assessment

The in-text and reference citations for the 4-week oral study in dogs cited as Block, 1987, should be corrected to Bloch, 1987.

There are two DPR (2009) references in the draft RCD. One references the “Guidance for Dietary Exposure Assessment” and is referred to as DPR (2009a) and the other references the “Notice of Decision to Initiate Reevaluation of Chemicals in the Nitroguanidine Insecticide Class of Neonicotinoids” and is referred to as DPR (2009b). The guidance document is referred to as DPR (2009b) on page 120 of the draft RCD, and is referred to as DPR (2009) on pages 101, 102 and 121 (two instances).

Page vii of the draft RCD (Reference Doses subsection of Executive Summary): The equation for the calculation of the reference dose is written incorrectly as (POD × % Abs). This should be (POD ÷ % Abs).

Page 7 of the draft RCD (Risk Characterization subsection of Technical Summary): The text references the dermal chronic RfD as a value 0.065 mg/kg-day. This value should be corrected to 0.059 mg/kg-day.

Page 37 of the draft RCD (Mammalian and Metabolism and Toxicokinetics subsection of Toxicokinetics in Toxicology Profile): The bullet beginning as ”Recovery in the urine of rats…” has an extra “in.”

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.

Page 73 of the draft RCD (Subchronic Neurotoxicity subsection of Neurotoxicity in Toxicology Profile): Typo in spelling of subchronic in very last sentence.

Page 80 and Table 21 of the draft RCD (Oral Developmental Neurotoxicity subsection of Neurotoxicity in Toxicology Profile): For Patel (2010), the text on page 80 and the text in Table 21 state two different NOELs/LOELs for maternal and developmental toxicity.

Page 81 of the draft RCD (Oral Developmental Neurotoxicity subsection of Neurotoxicity in Toxicology Profile): In Table 19, there are two “% Affected” rows after ”Male Pup PND 10 Abnormal Air Righting Reflex.” The data in the second “% Affected” row belong to the “Male Pup Wire Maneuver PND 10—Difficulty Grasping with Hind Legs” row at the

bottom of page 80. This row should be moved down to be with the appropriate "% Affected" data and to reflect the appropriate "N" data.

Page 82 of the draft RCD (Oral Developmental Neurotoxicity subsection of Neurotoxicity in Toxicology Profile): In Table 21, the NOEL and LOEL for developmental effects in Patel (2010) are incorrectly listed as 250 ppm (17.56 mg/kg-day) and 750 ppm (39.41 mg/kg-day), respectively. The developmental NOEL and LOEL should be corrected to 100 ppm (7.39 mg/kg-day) and 250 ppm (17.56 mg/kg-day), respectively.

Page 101 of the draft RCD (Introduction subsection of Dietary and Drinking Water Exposure in Exposure Assessment): In the equation used to calculate the total exposure of an individual for exposure to all foods, the summation symbol, ∑, is missing from the equation.

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 LD_{50} 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).

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.

B. Exposure Assessment

Content of Tables

- Some content was inaccurate – In Table 7, the dermal and inhalation average exposure values provided do not match the source values (DPR, 2007).
- Some content was mislabeled – In Table 19, under the column heading "Exposure[g] (µg/day)," all values appear to be default body weights for adult or child.

Typos

- Table 17, footnote e – cites a TC of 54,000. This conflicts with the value in the table.
- In Table 18 (footnote h) and Table 21 (footnote e), the acronym for hand surface area (HSA) appears as HAS.

Readability of Tables

- 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.

Accessibility Concerns

- DPR uses Times New Roman typeface, which is a serif font. The California Department of Rehabilitation recommends use of sans serif typefaces and font sizes to increase readability and accessibility.
- Footnote numbers within the tables were often smaller than 8 points. DPR should consider using a larger font size.

References

- OEHHA recommends that DPR add US EPA’s 2017 “Imidacloprid: Human Health Draft Risk Assessment for Registration Review” to the listed references. Currently, this document is only noted as an abbreviated reference in footnote “c” in Table 11.

V. REFERENCES

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VI. Appendix I. Data Tables for OEHHA's Evaluation and Calculation of the Imidacloprid Dermal Absorption Factor (DAF) Using Data from Odin-Feurtet (2009)

Table A1. Calculation of Imidacloprid Dermal Absorption Completion in Odin-Feurtet (2009)

Termination Time	8 hours Mean±SD	24 hours Mean±SD	72 hours Mean±SD	168 hours Mean±SD
Low Dose (0.5 g/L)				
Total % excreted[a]	0.342±0.189	1.967±0.954	2.749±0.775	3.067±0.945
Cardiac blood	ND	0.001±0.002	ND	ND
Non-treated skin	0.298±0.076	0.262±0.029	0.161±0.059	0.393±0.117
Carcass	1.476±0.425	0.806±0.132	0.704±0.062	0.488±0.227
Total % Directly Absorbed	2.116±0.668	3.037±0.841	3.614±0.736	3.947±1.145
% of Total Study Amount Absorbed[b]	**54%**	**77%**	**92%**	**-**
Intermediate Dose (70 g/L)				
Total % excreted	0.01±0.004	0.069±0.046	0.052±0.034	0.19±0.1
Cardiac blood	ND	ND	ND	ND
Non-treated skin	0.132±0.023	0.063±0.008	0.153±0.123	0.105±0.064
Carcass	0.282±0.062	0.228±0.041	0.275±0.026	0.26±0.041
Total % Directly Absorbed	0.425±0.062	0.36±0.081	0.48±0.115	0.554±0.166
% of Total Study Amount Absorbed	**77%**	**65%**	**87%**	**-**
Neat Product (350 g/L)				
Total % excreted	0.003±0.001	0.023±0.017	0.026±0.013	0.05±0.014
Cardiac blood	ND	ND	ND	0.017±0.015
Non-treated skin	0.086±1.813	0.06±0.007	0.078±0.007	0.086±0.017
Carcass	0.307±1.245	0.218±0.043	0.263±0.027	0.272±0.052
Total % Directly Absorbed	0.396±0.068	0.302±0.032	0.367±0.033	0.425±0.047
% of Total Study Amount Absorbed	**93%[c]**	**71%**	**86%**	**-**

[a] total % excreted is equal to the amount detected in urine, feces, and cage wash

[b] percent of total study amount absorbed at 8, 24, and 72 hours is equal to the total % directly absorbed at 8, 24, or 72 hours divided by the total % directly absorbed at 168 hours

[c] Data for one rat in the neat product group terminated at 8 hours was removed from calculations after being identified as an outlier when study authors noted a technical problem with the swabbing procedure for this animal.

N=4 rats/group

SD: Standard deviation; ND: Not detected

Table A2. Calculated Dermal Absorption Factor Using Mean Dermal Radioactivity Recovery Results for Low Dose (0.5 g/L) Imidacloprid Group (N=4 rats/group) from Odin-Feurtet (2009)

Termination Time	8 hours Mean±SD	24 hours Mean±SD	72 hours Mean±SD	168 hours Mean±SD
Total percent non-absorbed[a]	99.153±1.886	102.437±2.921	101.597±0.499	99.062±2.985
Total percent at application site[b]	2.248±0.719	1.173±0.241	0.571±0.115	0.876±0.607
Total percent directly absorbed[c]	2.116±0.668	3.037±0.841	3.614±0.736	3.947±1.145
DAF[d]	**4.364±1.08**	**4.209±1.054**	**4.186±0.728**	**4.823±1.565**

[a] sum of total percent swabs, surface dose, stratum corneum, fur and dressing
[b] sum of treated skin and surrounding skin
[c] sum of total percent excreted, cardiac blood, non-treated skin, and carcass
[d] sum of total percent at application site and total percent directly absorbed
DAF: Dermal absorption factor