CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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MEMORANDUM

TO: PCPA Imidacloprid Comments
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DATE: February 18, 2022

SUBJECT: OEHHA'S FINDINGS ON THE HEALTH EFFECTS OF IMIDACLOPRID RELEVANT TO ITS IDENTIFICATION AS A POTENTIAL GROUNDWATER CONTAMINANT

This memorandum serves as the written findings from the Office of Environmental Health Hazard Assessment (OEHHA) to the Pesticide Registration Evaluation Committee (PREC) subcommittee of the Department of Pesticide Regulation (DPR) for their consideration during the upcoming public hearing pertaining to imidacloprid product residue detections in groundwater. It also describes OEHHA's assessment of the proposed screening reference level put forth by DPR.

Summary of Review

A human health reference level (HHRL) of 283 parts per billion (ppb) for imidacloprid was determined by DPR (DPR, 2021a). This level was based on toxicity endpoints from a Risk Characterization Document (RCD) that is over 15 years old (DPR, 2006). Since the release of the 2006 RCD, a number of toxicity studies have become available that should be considered when determining a HHRL for imidacloprid, and assessing its risks. A review of the more recently published data indicates that imidacloprid can cause health effects in animal studies at doses lower than the point of departure (POD)

used in DPR's 2006 RCD. In addition, a re-evaluation of critical data sets from the 2006 RCD using newer methodology gave lower PODs for both acute and chronic endpoints. Based on our review, OEHHA has determined that the proposed HHRL of 283 parts per billion (ppb) is not health protective. We recommend that the PREC subcommittee, in evaluating the risks of imidacloprid in groundwater, select a lower screening level that has a sufficient margin of safety to protect against potential health risks of imidacloprid exposure through contaminated groundwater.

Background

On September 23, 2021, DPR issued a Legal Agricultural Use (LAU) determination for imidacloprid detections (DPR, 2021b). This action was triggered by detections above the reporting limit of 0.05 ppb for imidacloprid in DPR monitored groundwater wells. Under the California Pesticide Contamination Protection Act (PCPA) mandate, these detections have to be evaluated by a subcommittee of the PREC, consisting of one member each from DPR, OEHHA, and the State Water Resources Control Board (SWRCB) (DPR, 2021c). The subcommittee is tasked to review reports submitted by the registrant and any other information or data necessary to make the finding whether or not the legal agricultural use of imidacloprid has polluted or threatens to pollute California groundwater.

From 2014 to 2020, imidacloprid was detected above the reporting limit of 0.05 ppb in 15 wells, with concentrations ranging from 0.051 to 5.97 ppb. The LAU was preceded by an Updated Risks Memorandum (URM), released by DPR on April 13, 2021, which put forth an HHRL for imidacloprid in groundwater of 283 ppb to be used for screening human health concerns. The screening level proposed in the URM (DPR, 2021a) is based on toxicity values derived from the 2006 RCD for imidacloprid (DPR, 2006). The POD used to calculate the screening level was 5.5 milligrams per kilogram bodyweight per day (mg/kg-day), based on developmental neurotoxicity (DNT) in rats (Sheets, 2001). This value is an estimated-no-effect-level (ENEL) based on significant decreases in thickness of brain structures following exposure to 54.7 mg/kg-day for 32 days (21 days *in utero* and 11 days during lactation). The 2006 RCD and 2021 URM established that the most sensitive adverse effects of imidacloprid were neurotoxicity, DNT, and thyroid toxicity. Developmental and reproductive toxicity were also present in the database but were considered to occur at doses higher than those causing DNT. The memorandum also states that the critical PODs from the 2006 RCD are considered to be protective of all other effects for corresponding routes and durations.

Toxicity Evaluation

Several studies published in the open literature demonstrate adverse effects in multiple systems, including reproductive, developmental, and immunological, at doses lower than would elicit DNT (Table 1). While there is a large body of literature on imidacloprid

toxicity published since the last formal review in 2006, the focus of the evaluation presented here is to highlight the most sensitive published studies that indicate a hazard for imidacloprid in laboratory animals at or below the POD of 5.5 mg/kg-day used by DPR in the URM (DPR, 2021a).

Reproductive Toxicity

Evidence of male reproductive toxicity was observed in several studies significantly below the POD used by DPR of 5.5 mg/kg-day. Bal et al. (2012a) exposed adult male rats to imidacloprid for 90 days, and observed a significant decrease in sperm concentrations at 2 mg/kg-day. At 8 mg/kg-day, serum levels of testosterone, glutathione (GSH), and relative organ weights for the epididymis and seminal vesicles were decreased, and sperm motility was adversely affected. A parallel study in postnatal rats showed similar effects on reproductive parameters in developing animals (Bal et al., 2012b). Juvenile rats were exposed to imidacloprid for 90 days, after which testosterone levels and absolute epididymis weights were significantly decreased in dose groups as low as 0.5 mg/kg-day. In addition, the high dose group (8 mg/kg-day) showed decreased epididymal sperm number and increased abnormalities in sperm morphology.

Several similar endpoints were observed in a study by Zhao et al. (2021) in adult male rats exposed to low doses of imidacloprid for 90 days. A significant decrease in epididymal sperm concentration and testosterone levels were observed at 0.06 and 0.6 mg/kg-day, along with increased numbers of abnormal sperm. This study, along with many others in the recent literature, showed effects of imidacloprid at the lowest doses tested. When the data were amenable to modeling, Benchmark Dose (BMD) modeling was conducted to derive potential PODs that could be used for deriving a health protective concentration for groundwater. OEHHA modeled the effects of imidacloprid on sperm concentration from Zhao et al. (2021) with a benchmark response (BMR) of 1 standard deviation (SD) and returned a POD (calculated as a $BMDL_{1SD}$) of 0.02 mg/kg-day.

In another reproductive toxicity study, adult male mice were exposed to imidacloprid for 28 days (Bagri et al., 2015). At 14 days post-dosing, sperm head abnormalities were significantly increased at 5.5 mg/kg-day, the lowest dose tested in the study. Following mating with non-exposed females, a significant increase in fetal death was observed at 6 weeks post-mating, but only in the highest dose group of 22 mg/kg-day. Benchmark dose modeling of sperm head abnormalities at 14- and 21-days returned PODs (calculated as a $BMDL_{1SD}$) of 0.6 and 0.7 mg/kg-day, respectively.

An additional study published in the literature exposed both juvenile and adult rats to a single dose of 1 mg/kg-day of imidacloprid (Abdel-Rahman Mohamed et al., 2017). This study showed decreased relative seminal vesicle and testes weights, decreased sperm

concentration and motility, and increased incidence of abnormal sperm. The use of only a single dose limits this study's use, but it provides additional evidence of reproductive effects at doses below the POD used by DPR (DPR, 2021a).

Immunotoxicity

The POD used by DPR based on DNT is likely not protective against the immunotoxic effects of imidacloprid. A study investigating the immunological response in mice following oral exposure to imidacloprid (Badgujar et al., 2013) found an altered response to delayed-type hypersensitivity (DTH). DTH is an inflammatory response to an antigen challenge, measured by swelling at the injection site and histopathological changes in the affected tissue. Female mice were treated with 2.5, 5.0, or 10 mg/kg-day imidacloprid for 28 days. On day 28, the mice were challenged using sheep red blood cells as an antigen, and swelling was measured at 24 and 48 hours post-challenge. In the high dose group, a significant decrease in DTH at 24 hours was observed, while decreased DTH and decreased histopathological indices of inflammation were observed at 48 hours in the 5 and 10 mg/kg-day dose groups. The no-observed-adverse-effect level (NOAEL) from this study was 2.5 mg/kg-day for the immunosuppressive effects of imidacloprid, approximately 2-fold lower than the POD of 5.5 mg/kg-day used by DPR. BMD modeling of decreased DTH at 48 hours with a BMR of 1 SD returned a POD (calculated as a $BMDL_{1SD}$) of 0.8 mg/kg-day.

Developmental Neurotoxicity

There is also evidence from the literature of more sensitive DNT effects than the POD used by DPR. A study by Kara et al. (2015), exposed post-natal and adult male rats to imidacloprid for 90 days. This study showed DNT effects at 2 mg/kg-day in pups, including delayed latency in the Morris water maze on days 3, 4 and 5 of training, exhibiting both statistical significance and dose response. Adults in the study were less sensitive than pups, with similar effects observed following imidacloprid exposure but occurring at the next highest dose (8 mg/kg-day), and only on days 4 and 5.

Neurotoxicity

Khalil et al. (2017) demonstrated decreased motor activity and increased rearing and freezing behaviors in an open field test, and decreased swimming time in the forced swim test, in adult male rats following 60 days of imidacloprid exposure at doses of 0.5 and 1.0 mg/kg-day. The high dose of 1.0 mg/kg-day imidacloprid also caused increased grooming behaviors and increased levels of serum cortisone and norepinephrine levels. The study lacked a NOAEL because effects were seen at both doses tested. BMD analysis of several endpoints from this study produced PODs (calculated as a $BMDL_{1SD}$) ranging from 0.05 to 0.3 mg/kg-day. The lowest POD of 0.05 mg/kg-day was derived from decreased swim time in the forced swimming test. The functional neurobehavioral effects observed in this study demonstrate statistical

significance and dose response, and appear to be more sensitive indicators of imidacloprid neurotoxicity than studies evaluated in the 2006 RCD.

Glucose Homeostasis

In addition to neurotoxicity as described above, Khalil et al. (2017) also observed increased levels of serum glucose and decreased levels of insulin in both adult and juvenile male rats treated with 1.0 mg/kg-day imidacloprid. Alterations in glucose levels (hyperglycemia) and insulin resistance were observed in two additional studies in mice. Adult male (Sun et al., 2016) and female (Sun et al., 2017) mice were exposed to 0, 0.06, 0.6, or 6 mg/kg-day imidacloprid for 84 days. The mice were fed a control or high fat diet in conjunction with imidacloprid exposure. Increased body weight, adipose tissue weights and adipocyte size occurred in the high fat diet group of imidacloprid exposed mice at 0.06 mg/kg-day in males and 0.6 mg/kg-day in females. In males, insulin levels were increased at all doses following 11 weeks of exposure, and glucose intolerance was increased at the highest dose tested. Females also had higher insulin levels, but only at the high dose. In the control diet group, effects of imidacloprid at the lowest doses were minimal and often lacked dose response. Due to the effects being pronounced only in the high fat diet group and the lack of dose response and statistical significance for most endpoints in the control diet group, these studies were included for supplemental support and not for POD consideration.

Studies from the 2006 RCD

In addition to the newer studies identified here, a re-evaluation of critical data sets from the 2006 RCD gave lower PODs for both chronic and acute endpoints. For chronic exposure, the 2006 RCD chose increased incidence of mineralized particles in the thyroid gland of male rats as the critical effect (Eiben and Kaliner, 1991) and a NOAEL of 5.7 mg/kg-day was used to derive a health protective value. DPR did not conduct BMD analysis for this endpoint in the 2006 RCD but OEHHA determined that the dataset is amenable to modeling. Using BMDS 3.2 for the analysis, a POD (calculated as the 95% lower confidence limit on the benchmark dose of the 5% effect level or $BMDL_{05}$) of 1 mg/kg-day was derived (Appendix 1).

The 2006 RCD selected the acute neurotoxicity study in rats (Sheets, 1994) as the critical study for acute exposure to the general population, while the DNT study in rats (Sheets, 2001) was used for acute exposures in women of child bearing age. The acute neurotoxicity data showed decreased motor and locomotor function in both males and females at 90 minutes post-dosing with a NOAEL was 42 mg/kg-day. Using the BMD software at the time (BMDS 1.3.2), the POD (calculated as the lower 95% confidence limit of the effective dose or LED_{05}) was 9 mg/kg-day. BMDS software has undergone many improvements and updates since its inception, and the older versions may yield different results than newer versions. OEHHA modeled the same data using the most

recent BMDS version (BMDS 3.2) and similar parameters as the 2006 RCD (5% relative deviation and non-constant variance), and derived a POD (calculated as a $BMDL_{05}$) of 4.66 mg/kg-day, or half the value derived in 2006 (Appendix 2). This value, based on the same data set, is more health protective than the previous PODs for all populations.

Table 1: Lowest-observable-adverse-effect levels (LOAELs) from animal studies of imidacloprid toxicity identified from the open literature with effects observed at doses lower than the POD used by DPR to calculate their HHRL

Evidence type	**Study description**	**Critical Effects**	**LOAEL**	**Reference**
Reproductive toxicity	Adult and juvenile male rats were exposed by gavage to 0 and 1 mg/kg-day imidacloprid for 65 days	Decreased body weight, seminal vesicle and testicular indexes, testosterone, sperm concentration, motility and viability; increased abnormal sperm	1 mg/kg-day	Abdel-Rahman Mohamed et al., 2017
Reproductive toxicity	Adult male rats were exposed by gavage to 0, 0.5, 2, and 8 mg/kg-day imidacloprid for 90 days	Decreased sperm concentration and motility, reduced body weight gain, reduced relative organ weights for the epididymis and seminal vesicles, decreased testosterone	2 mg/kg-day	Bal et al., 2012a
Reproductive and developmental toxicity	Newborn male rats (7 days old at start of experiment) were exposed by gavage to 0, 0.5, 2, and 8 mg/kg-day imidacloprid for 90 days	Decreased body weight, serum testosterone, and absolute epididymis and cauda epididymis weights (all doses), decreased sperm concentration and increased abnormal sperm (high dose)	0.5 mg/kg-day	Bal et al., 2012b
Reproductive toxicity	Male mice were exposed orally to 0, 5.5, 11, 22 mg/kg-day imidacloprid for 7, 14, and 28 days	Increased frequency of abnormal sperm at 14 days and 28 days of treatment	5.5 mg/kg-day	Bagri et al., 2015
Reproductive toxicity	Adult male rats were exposed by gavage to 0, 0.06, and 0.6 mg/kg-day imidacloprid for 90 days	Decreased serum testosterone, sperm concentration, and increased sperm abnormalities	0.06 mg/kg-day	Zhao et al., 2021

Immunotoxicity	Adult female mice were exposed by gavage to 0, 2.5, 5, and 10 mg/kg-day for 28 days	Decreased delayed-type hypersensitivity at 48 hours post-challenge	5 mg/kg-day	Badgujar et al., 2013
Developmental neurotoxicity	Adult and newborn male rats were exposed by gavage to 0, 0.5, 2, and 8 mg/kg-day imidacloprid for 90 days	Delayed latency in Morris maze starting on day 3 of training for pups; starting on day 4 of training for adults	Pups: 2 mg/kg-day Adults: 8 mg/kg-day	Kara et al., 2015
Neurotoxicity and Glucose Homeostasis	Adult and juvenile male rats were exposed by gavage to 0, 0.5 and 1.0 mg/kg-day for 60 days	Decreased motor activity, increased rearing and grooming, increased levels of serum glucose, cortisone and norepinephrine, decreased levels of insulin	0.5 mg/kg-day	Khalil et al., 2017
Glucose Homeostasis	Adult male mice were exposed to 0, 0.06, 0.6, and 6 mg/kg-day by gavage for 84 days	Increased body weight, increased adipose tissue weights in conjunction with a high fat diet, increased insulin resistance, and altered glucose homeostasis	0.06 mg/kg-day	Sun et al., 2016
Glucose Homeostasis	Adult female mice were exposed to 0, 0.06, 0.6, and 6 mg/kg-day by gavage for 84 days	Increased body weight, increased adipose tissue weights and adipocyte size in conjunction with a high fat diet at the mid dose, increased insulin resistance at the high dose	0.6 mg/kg-day	Sun et al., 2017

Abbreviations: Point of departure (POD); Human health reference level (HHRL); Milligrams per kilogram body weight per day (mg/kg-day).

Comparison of Toxicity Endpoints

Although some of these newer studies may have shortcomings that limit their utility as critical studies, the overall evidence in the imidacloprid toxicity database published since the last evaluation done for the 2006 RCD indicates that the 5.5 mg/kg-day POD used by DPR (2021a) is not likely protective of potential health effects due to exposure to imidacloprid. That POD is higher than the effect levels for serious health effects observed in a number of studies.

Figure 1 further demonstrates the lack of health protectiveness of relying on the 2006 data and analysis. It compares the ENEL from the critical study used by DPR in the URM (Sheets, 2001 as cited in DPR, 2021a) with PODs from the studies presented in Table 1. PODs for each study were either NOAELs, ENELs, or BMDLs when available. ENELs were derived by the conventional practice of applying an uncertainty factor of 10 to the LOAEL for studies with effects at the lowest doses.

Figure 1: Comparison of points of departure from recent animal toxicity studies of imidacloprid

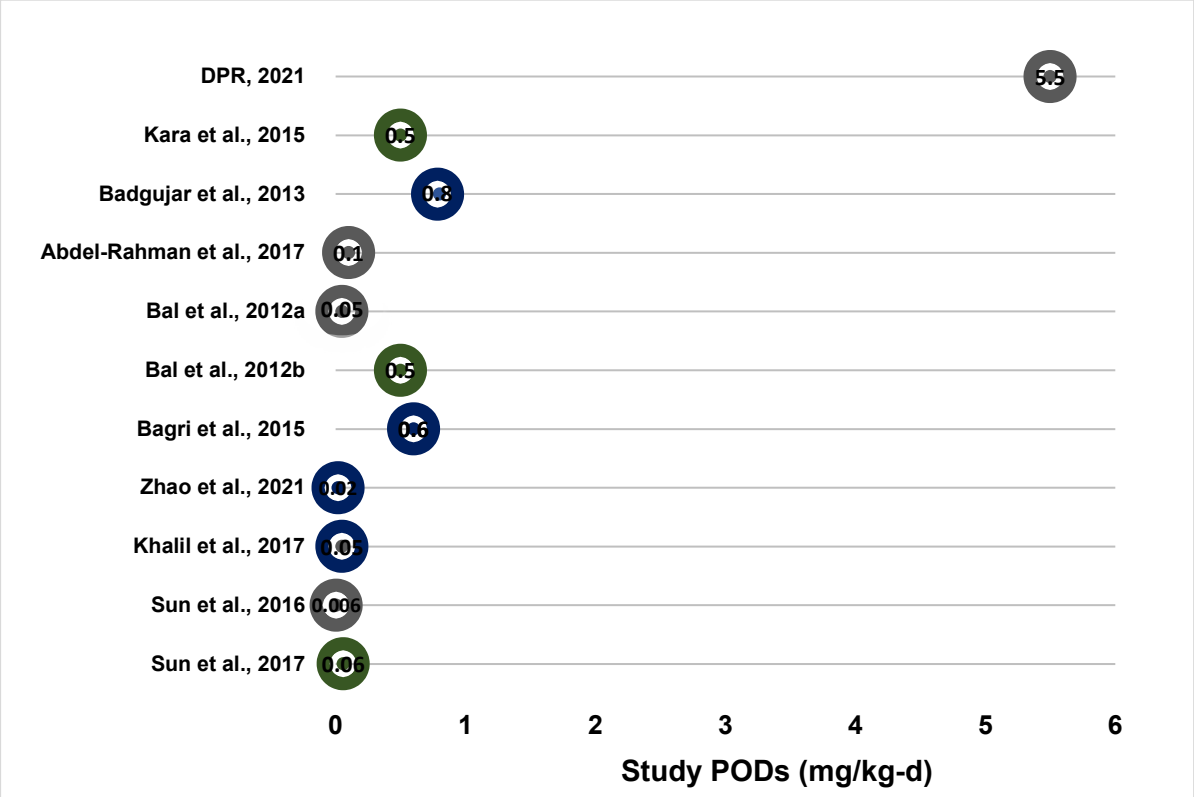

Figure Legend: BMDL (blue data points); ENEL (grey data points); NOAEL (green data points)

Additionally, there are precedents for other regulatory agencies utilizing these recent published toxicity studies for risk assessment. Minnesota Department of Health (MDH)

chose immunotoxicity from Badgujar (2013) as their critical study to derive a short-term non-cancer health based guidance value for water of 2 µg/L (MDH, 2020). Health-based values are defined by the MDH as a level of a contaminant that would pose little or no health risk to a person consuming that water. The values are only based on potential health risks and do not consider economic or other factors. This is similar to how OEHHA derives our Public Health Goals – guidance levels for assessing risks of drinking water (PHG). The POD used by MDH of 0.820 mg/kg-d was derived from BMD modeling of decreased DHT at 48 hours post-challenge. This was lower than the NOAEL of 2.5 mg/kg-day for the study.

The Wisconsin Department of Health Services chose Sun et al. (2016) as their critical study and derived an enforcement standard for imidacloprid in water of 0.2 µg/L (WDHS, 2019). This was based on the lowest observable adverse effect level (LOAEL) of 0.06 mg/kg-day for effects on weight gain, adipose cell size, and effects on glucose levels and kidney weights. The preventative action limit, which would be more similar to a screening level value to prevent contamination, was set to 10% of the enforcement level, or 0.02 µg/L.

Potential Public Health Screening Levels

For the subcommittee's consideration, OEHHA derived alternative candidate public health protective concentrations (PHC) for imidacloprid in drinking water from the recent toxicity studies described above. OEHHA defines the PHC as the concentration of a chemical in drinking water that is not expected to pose a significant risk to health, when consumed either for a short-term duration, or over a lifetime. OEHHA develops these potential PHCs using approaches and methods from OEHHA's PHG Program. Generally speaking, the PHC is derived by calculating an average daily dose (ADD), which is the POD divided by the uncertainty factor (UF). The ADD is then multiplied by the relative source contribution (RSC), and divided by the appropriate drinking water intake (DWI) rate.

$$ADD = \frac{POD}{UF}$$

$$PHC = \frac{ADD \times RSC}{}$$

OEHHA's methodology for developing PHCs differ from DPR's methodology for developing HHRLs. DPR derives the HHRL by calculating the residue level in drinking water that gives the 95th percentile margin of exposure (MOE) at the target MOE for the target population, using the critical POD. In the case of imidacloprid, DPR chose a target MOE of 100 and a target population of non-nursing infants. Using US EPA's Dietary Exposure Evaluation Model (DEEM), the acute and chronic 95th percentile exposures were estimated for bottle fed infants. When calculating the acute and chronic

MOEs, the highest detected level of imidacloprid was used (5.97 ppb). The HHRL was then calculated as the residue in drinking water that would result in a 95th percentile MOE at the target MOE (100), using the critical POD of 5.5 mg/kg-day (DPR, 2021a). This resulted in DPR's HHRL for imidacloprid of 283 ppb.

When developing health protective levels for noncancer effects based on animal toxicity studies, OEHHA generally applies a combined UF of 300 (OEHHA, 2008). A factor of 10 is used to account for toxicokinetic and toxicodynamic differences in response between laboratory animals and humans (interspecies UF). A factor of 30 is applied to account for differences in response between humans (intraspecies UF). This factor considers that some subpopulations, such as children or the elderly, may be more sensitive to the chemical than the general population. For the developmental and reproductive animal toxicity studies described in Table 1, the intraspecies UF was reduced from 30 to 10 as studies were conducted in juvenile and adult lifestages and differences in susceptibility are adequately characterized.

For imidacloprid, the default RSC of 20% was used for acute exposures since it is anticipated that infants aged 0-12 months are the most sensitive subpopulation, and significant exposure to imidacloprid will occur through sources other than drinking water. Infants in that age range typically consume solid foods in addition to milk or formula, and exposures via environmental sources, such as flea and tick treatments on family pets, can occur. For chronic exposure, a default RSC of 20% was also applied since the majority of exposure over a lifetime is expected to occur through dietary sources stemming from agricultural use, and from household use of imidacloprid as an insecticide.

For oral DWI, OEHHA used age specific water ingestion estimates (OEHHA, 2012), normalized to body weight. DWI is expressed in liters or liters equivalent per kilogram of body weight per day (L/kg or L_{eq}/kg-day, respectively). Liters equivalent represents the equivalent of the amount of drinking water one would have to drink to account for the exposure to a chemical in tap water through oral, inhalation, and dermal routes. However, due to the physiochemical properties of imidacloprid, inhalation and dermal exposure through household uses of water are expected to be negligible. For acute scenarios, OEHHA applied a DWI rate of 0.288 L/kg-day for infants aged 0-12 months old, as they the most sensitive subpopulation due to water intake rate relative to body weight. For chronic scenarios, OEHHA applied a lifetime averaged DWI rate of 0.053 L/kg-day.

Using the appropriate UFs, a RSC of 0.2, and DWI of 0.053 L/kg-day (lifetime) or 0.288 L/kg-day (acute), candidate PHC's for imidacloprid using various toxicity endpoints as compared to DPR's proposed HHRL are presented for the subcommittee's consideration in Table 2. The studies selected for PHC derivation were found to be of sufficient quality and reporting, and had points of departure ranging from 0.05 to 1

mg/kg-day. The calculated PHCs ranged from 2 ppb to 23 ppb, significantly lower than the HHRL calculated by DPR (2021a).

Table 2: Potential public health concentrations derived from critical PODs identified by OEHHA from an updated toxicity review

POD	Study Type	Study Endpoint	Total UF	DWI	PHC
0.05 mg/kg-day	Neurotoxicity and Glucose Homeostasis	Khalil et al., 2017 $BMDL_{1SD}$ for decreased swim time in forced swimming test	100	0.053 L/kg-day chronic	1.9 µg/L or 2 ppb (rounded)
0.5 mg/kg-day	DNT	Kara et al., 2015 NOAEL for delayed latency in Morris maze in postnatal rat pups	100	0.228 L/kg-day acute	4.4 µg/L or 4 ppb (rounded)
0.5 mg/kg-day	Reproductive Toxicity	Bal et al., 2012a NOAEL for sperm and reproductive effects in adult rats	100	0.053 L/kg-day chronic	18.9 µg/L or 19 ppb (rounded)
0.6 mg/kg-day	Reproductive Toxicity	Bagri et al., 2015 $BMDL_{1SD}$ for increased sperm head abnormalities in male mice with 21 days of treatment	100	0.053 L/kg-day chronic	22.6 µg/L or 23 ppb (rounded)
0.8 mg/kg-day	Immunotoxicity	Badgujar et al., 2013 $BMDL_{1SD}$ for decreased DTH at 48 hours post-challenge	300	0.053 L/kg-day chronic	10.1 µg/L or 10 ppb (rounded)
1 mg/kg-day	Chronic Toxicity	Eiben and Kaliner, 1991 $BMDL_{05}$ for incidence of mineralized particles in thyroid gland of male rats	300	0.053 L/kg-day chronic	12.6 µg/L or 13 ppb (rounded)

Abbreviations: Point of departure (POD); Uncertainty Factor (UF); Drinking water intake (DWI); Public health concentration (PHC); Developmental neurotoxicity (DNT); Estimated-no-effect level (ENEL); Margin of exposure (MOE); Parts per billion (ppb); Human health reference level (HHRL); Liters per kilogram body weight per day (L/kg-day); Microgram per liter (µg/L); No-observable-adverse-effect level (NOAEL); Milligrams per kilogram body weight per day (mg/kg-day); Delayed-type hypersensitivity (DTH).

Conclusions

As outlined in this memorandum, the published literature in recent years shows lower critical toxicity endpoints compared to what DPR used in the URM (DPR, 2021a) and the Imidacloprid RCD (DPR, 2006). These newer toxicity studies demonstrate numerous significant effects in laboratory animals at doses ranging from the current critical POD of 5.5 mg/kg-day, down to 0.06 mg/kg-day, representing an almost 100-fold range below the value used by DPR. OEHHA recommends that the PREC subcommittee select a more health protective screening level than the HHRL proposed in the URM (DPR, 2021a). This could be accomplished by selecting an alternative PHC from Table 2 above, or by utilizing an alternative method by the subcommittee. We thank the PREC subcommittee for considering the evidence provided by OEHHA.

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Appendix 1: BMDS – Imidacloprid-Induced Mineralization of the Colloid of Thyroid Follicles in Rats (Eiben and Kaliner, 1991) using a BMR of 5% relative deviation

User Input

Info

Model	frequentist Log-Logistic v1.1
Dataset Name	DataSet Name1
User notes	[Add user notes here]

Dose-Response Model P[dose] = g+(1-g)/[1+exp(-a-b*Log(dose))]

Model Options

Risk Type	Extra Risk
BMR	0.05
Confidence Level	0.95
Background	Estimated

Model Data

Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	5

Model Results

Benchmark Dose

BMD	2.237531905
BMDL	1.013712541
BMDU	4.103117251
AIC	274.6716587
P-value	0.43695588
D.O.F.	2
Chi2	1.655846098

Model Parameters

# of Parameters	3

Variable	Estimate
g	0.133856331
a	-4.13494285
b	1.478201075

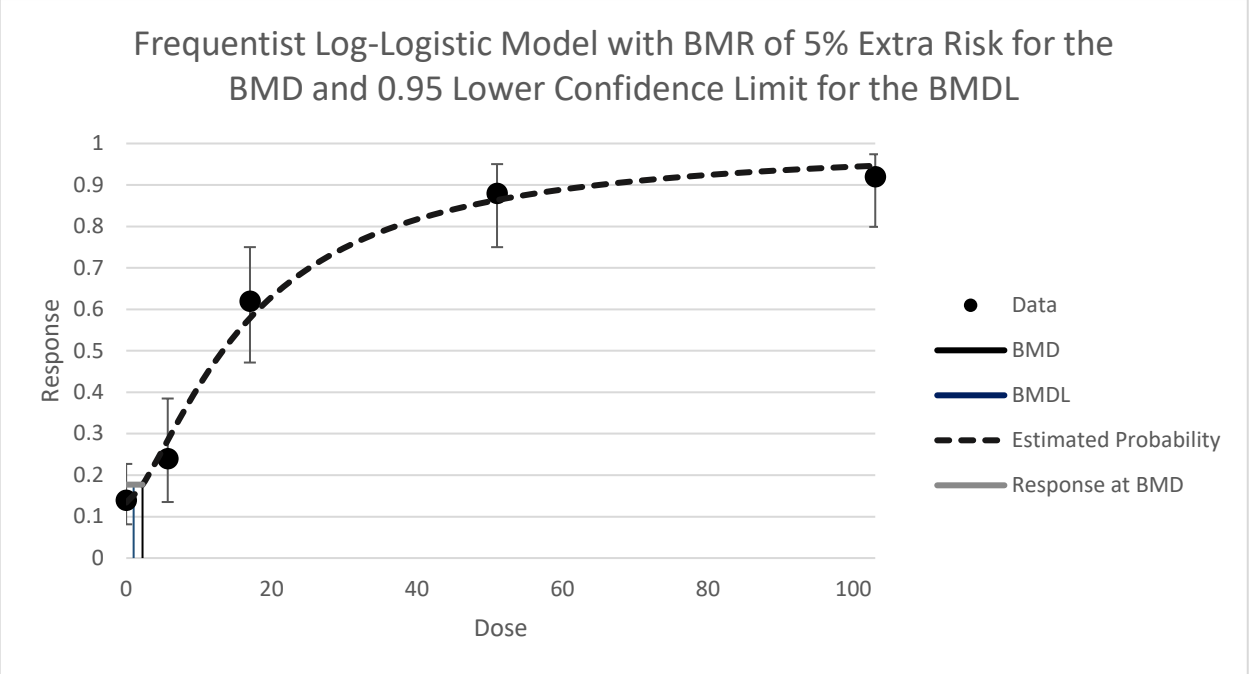
Goodness of Fit

Dose	Estimated Probability	Expected	Observed	Size	Scaled Residual
0	0.133856331	13.3856331	14	100	0.180432

5.7	0.283988043	14.19940214	12	50	-0.689778	
	17	0.578427019	28.92135093	31	50	0.595299
	51	0.863598212	43.17991058	44	50	0.337917
	103	0.94627405	47.31370252	46	50	-0.82397

Analysis of Deviance

Model	Log Likelihood	# of Parameters	Deviance	Test d.f.	P Value
Full Model	-133.538269	5	-	-	NA
Fitted Model	-134.335829	3	1.59511991	2	0.450427
Reduced Model	-207.88415	1	148.691762	4	<0.0001



Appendix 2: BMDS – Imidacloprid-Induced Decrease in Motor Activity in Adult Female Rats (Sheets' 1994) using a BMR of 5% relative deviation

User Input

Info

Model	frequentist Hill v1.1
Dataset Name	DataSet Name1
User notes	[Add user notes here]

Dose-Response Model	M[dose] = g + v*dose^n/(k^n + dose^n)
Variance Model	Var[i] = alpha * mean[i] ^ rho

Model Options

BMR Type	Rel. Dev.
BMRF	0.05
Tail Probability	-
Confidence Level	0.95
Distribution Type	Normal
Variance Type	Non-Constant

Model Data

Dependent Variable	[Custom]
Independent Variable	[Custom]
Total # of Observations	4
Adverse Direction	Automatic

Model Results

Benchmark Dose

BMD	9.24325868
BMDL	4.65835206
BMDU	54.7347738
AIC	593.992102
Test 4 P-value	0.49288454
D.O.F.	1

Model Parameters

# of Parameters	6

Variable	Estimate
g	499.477389
v	-732.32966
k	261.804547
n	Bounded

rho 1.68188511
alpha 0.41666415

Goodness of Fit

Dose	Size	Estimated Median	Calc'd Median	Observed Mean	Estimated SD	Calc'd SD	Observed SD	Scaled Residual
0	12	499.47739	504	504	228.968	262	262	0.06842
42	12	398.23517	366	366	189.254	194	194	-0.59
151	12	231.59812	263	263	119.973	93	93	0.9067
307	10	104.21823	96	96	61.2988	71	71	-0.424

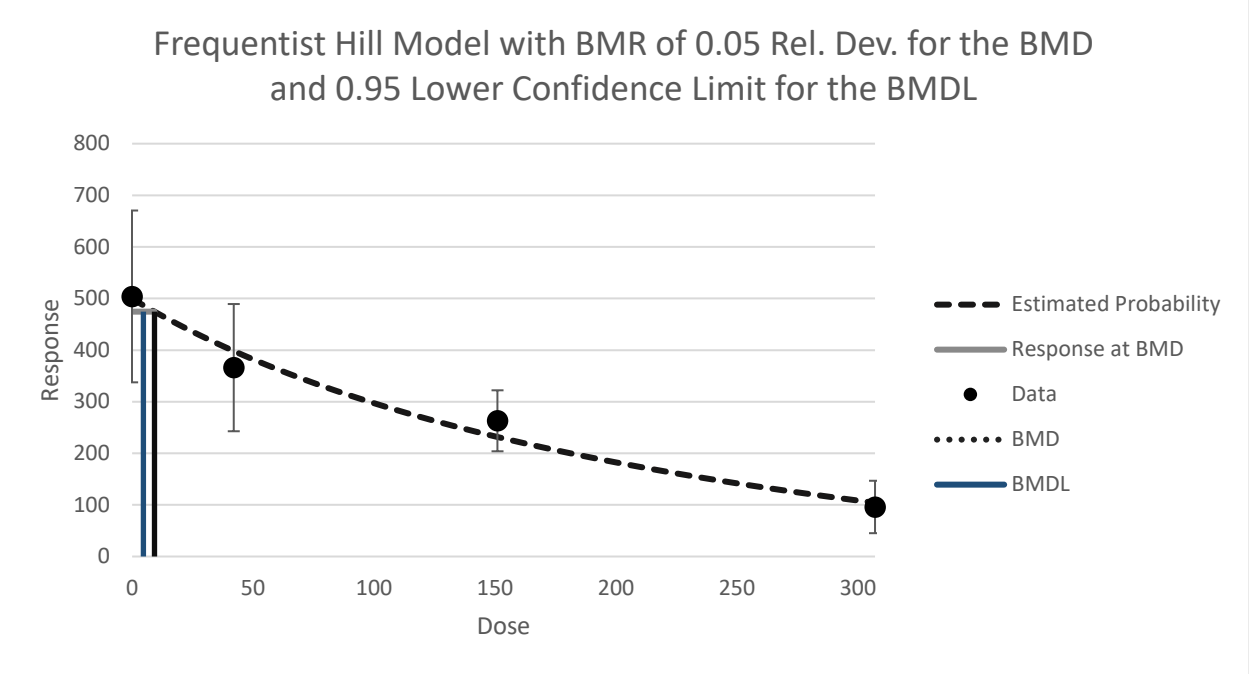
Likelihoods of Interest

Model	Log Likelihood*	# of Parameters	AIC
A1	-301.17255	5	612.345
A2	-290.23059	8	596.461
A3	-291.76094	6	595.522
fitted	-291.99605	5	593.992
R	-313.93947	2	631.879

* Includes additive constant of -42.27117. This constant was not included in the LL derivation prior to BMDS 3.0.

Tests of Interest

Test	-2*Log(Likelihood Ratio)	Test df	p-value
1	47.4177628	6	<0.0001
2	21.8839258	3	<0.0001
3	3.06069957	2	0.21646
4	0.47022312	1	0.49288


Frequentist Hill Model with BMR of 0.05 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL
Response
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
300
Dose
Estimated Probability
Response at BMD
Data
BMD
BMDL