Pesticide Exposure and Risk Assessment

Document Review

Department of Pesticide Regulation's Draft Risk Characterization and Exposure Assessment Documents for Propanil

Pesticide and Environmental Toxicology Branch
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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 (HEAD), which describes non-dietary exposure scenarios and estimates exposure levels of workers and residents.

This report is a review of the draft RCD for the pesticide propanil provided by DPR (dated and received December 30, 2016). The draft HEAD was included as Appendix D in the draft RCD.

This peer review report has five parts:

    I.   Summary of Review
    II.   Major Comments
    III.   Response to Charge Statements
    IV.   Detailed Comments
    V.   Minor Comments

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I. SUMMARY OF REVIEW

This report presents the review by the Office of Environmental Health Hazard Assessment (OEHHA) on the Department of Pesticide Regulation's (DPR) draft Risk Characterization Document (RCD) for propanil, a post-emergence herbicide currently registered for rice production. The draft RCD characterized human health risks from exposures to propanil in the diet and drinking water (oral), from occupational activities (dermal and inhalation), and from spray-drift after application to air (dermal and inhalation). Aggregate exposures for workers and the bystanders (oral, dermal, and inhalation) were also addressed. The durations evaluated were acute, subchronic, and chronic exposures.

Overall, we find the document well written with extensive and complete descriptions of the toxicological profile and exposure assessments. While the rationale for the non-cancer endpoint and point of departure (POD) selection was clearly presented, we recommend increasing the overall uncertainty factor (UF) to protect sensitive populations (e.g., infants and small children) against methemoglobinemia and a database deficiency factor for one of its key metabolites, 3,4-dichloroaniline (3,4-DCA). Based on the genotoxic and carcinogenic information on propanil and 3,4-DCA, we are concerned about the carcinogenic effects of propanil and suggest DPR to use the non-threshold approach in evaluating the cancer risk from lifetime exposure.

Our major comments are summarized in Section II. Responses to DPR's charge statements are provided in Section III. Detailed comments for the entire document are provided in Section IV and minor comments are in Section V.

II.   MAJOR COMMENTS

Our major comments are grouped into A) Toxicity Evaluation and Risk Assessment and B) Exposure Assessment.

A. Toxicity Evaluation and Risk Assessment

1. Non-cancer Endpoint Selection and Point of Departure Determination

a. Toxicity Endpoint

- o Known adverse effects for propanil and 3,4-DCA were adequately covered in the description of the toxicity studies. All the PODs were based on propanil even when 3,4-DCA was the dominant chemical in the dietary exposure of the general population. 3,4-DCA is an environmental degradant of propanil and has been detected in rice. For this exposure scenario, DPR converted 3,4-DCA in rice to propanil-equivalent based on a molecular weight ratio of 1.35. Since there are dermal and developmental toxicity study data indicating that 3,4-DCA may be more toxic than propanil, OEHHA recommends DPR discuss the potential underestimation of the risk from the approach used in the draft RCD and consider including an additional uncertainty factor (UF) for database deficiency when assessing health risks from exposure to 3,4-DCA.

b. Benchmark Dose Modeling

- o OEHHA agrees with the use of benchmark dose (BMD) modeling, which is preferred over the more traditional NOEL/lowest-observed-effect level (LOEL) approach for determining POD when the data are amenable to modeling.

- o OEHHA also agrees with using a default benchmark response (BMR) of one standard deviation (1SD) for modeling continuous data when the biological relevance of a given percentage change is not clear. However for quantal or incidence data, OEHHA recommends a default BMR of 5% instead of the BMR of 10%. This approach should yield lower limits of the benchmark dose (BMDL) values that are close to the NOEL of the study.

c. Oral Toxicity Evaluation

- DPR selected an acute oral POD of 14.2 milligrams per kilogram-day (mg/kg-day) for increased methemoglobin (metHb) levels following 5 days of dietary exposure to propanil in a short-term rat feeding study (O'Neill, 2002). While OEHHA agrees with this selection, OEHHA recommends that DPR provide justification for not selecting the lower POD of 8.9 mg/kg-day for the decrease in body weight gain observed in the first week of the chronic dietary rat study (Bellringer, 1994).

- DPR selected the subchronic oral POD of 5 mg/kg-day based on increased metHb levels following 13 weeks of propanil exposure in the chronic dietary rat study (Bellringer, 1994). OEHHA agrees with the selection because the low dose (9 mg/kg-day) is close to the BMDL (5 mg/kg-day), there is less uncertainty in identifying the BMDL, and its identification is less dependent on model selection.

- For the chronic oral POD, DPR chose the $BMDL_{10}$ of 0.5 mg/kg-day for male spleen hemosiderosis from the chronic dietary rat study (Bellringer, 1994). OEHHA has several concerns with using this endpoint as the critical effect (see Detailed Comments in Section IV.C.3). Thus, OEHHA recommends re-analysis of the hemosiderosis data or consideration of other endpoints, such as determining "total pericholangitis" in the liver from the same study as the critical effect.

d. Inhalation Toxicity Evaluation

- Since there were no appropriate inhalation toxicity study of propanil available, DPR used the oral PODs for route-to-route extrapolation and assumed 100 percent inhalation absorption. Based on the available data, OEHHA agrees with the approach and the methods used in evaluating inhalation exposures.

- However, DPR described a 14-day inhalation study of 3,4-DCA with a NOEL that was lower than the subchronic oral POD and reported effects of metHb at all doses tested. If possible, OEHHA suggests DPR obtain and evaluate this inhalation study and determine if there is any potential inhalation exposure of workers or residents to 3,4-DCA.

e. Dermal Toxicity Evaluation

- Since there were no appropriate dermal toxicity studies available, DPR used the oral PODs to assess dermal exposure. OEHHA agrees with this approach.

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2. Carcinogenicity Weight of Evidence

o DPR concluded that the evidence was insufficient to calculate a cancer potency for propanil, citing a lack of strong positive genotoxicity and a lack of dose-response relationships in the animal data. OEHHA disagrees with this conclusion. Based on the cancer bioassay data of propanil and genotoxicity data of propanil and 3,4-DCA, OEHHA believes there is sufficient evidence to show propanil causes carcinogenic effects. There are statistically significant positive dose-response relationships for three tumor types in two animal species (benign testicular interstitial tumors in male rats, hepatocellular adenomas in female rat and male mice, and malignant lymphoma in spleen of female mice).

o OEHHA recommends that a quantitative risk assessment be conducted using the default non-threshold approach (low dose linear extrapolation) to evaluate the cancer risk from lifetime exposure to propanil.

3. Uncertainty Factors and Sensitive Populations

o Since all the PODs were derived from laboratory animal studies, DPR applied a 10-fold interspecies UF based on the assumption that humans could be 10 times more sensitive than animals. OEHHA agrees with the application of this UF.

o DPR applied an UF of 10 for intraspecies variability. OEHHA recommends the use of a default UF of 30 to account for intraspecies variability. We note that a larger total UF of 300, compared to the conventional total UF of 100, is particularly needed because the critical effect is an increase in blood metHb. Infants and small children are known to be more susceptible than adults to methemoglobinemia, and a larger UF therefore is warranted to ensure protection of this sensitive subpopulation.

4. Risk Characterization

o 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.

o When the exposure is to 3,4-DCA, the MOE should be calculated based on PODs derived for 3,4-DCA, when possible. If these studies are not

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available, OEHHA recommends addition of a database UF for these scenarios.

o   The subchronic POD (5 mg/kg-day) was used to calculate the MOE for annual occupational exposure. OEHHA recommends using the chronic POD for the calculation because the annual exposure was an estimate of exposure spread over the year.

B. Exposure Assessment

1. Document Organization

o   The organization of the exposure assessment within the draft RCD – with a dietary exposure assessment section in the main document, a separate appendix for occupational and residential exposure assessment, and a technical appendix that presented results of modeled spray drift exposure – is difficult to follow and needs to be improved. OEHHA recommends that DPR describe the exposure assessment either as a separate section in the RCD or a stand-alone report.

2. Occupational Exposure

o   To account for scenario-specific personal protective equipment (PPE) and engineering controls, DPR applied "adjustment factors" to generic mean exposure values from the Pesticide Handler Exposure Database (PHED). These adjusted mean exposure values were further modified using a statistical approach developed by DPR to generate high-end estimates of acute, seasonal, annual and lifetime absorbed daily doses (ADDs) for inhalation and dermal exposure pathways. OEHHA agrees with this approach; however, we recommend that the specific PPE adjustments for the aerial applicator scenario be reviewed and revised if necessary, as OEHHA's estimate of the acute ADD was more than three-fold higher than the value reported in the Human Exposure Assessment Document (HEAD). OEHHA also suggests that the HEAD include more details on how the PPE adjustment factors were applied.

o   The propanil HEAD also presented post-application exposure estimates for two occupational activities, "scouting" and "weeding." Because propanil-specific dislodgeable foliar residue (DFR) dissipation data were unavailable, dermal exposure was estimated using a default transfer coefficient and a default DFR as recommended by US Environmental Protection Agency (US EPA) guidance. OEHHA agrees with this

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approach. However, we found that the default DFR (calculated by assuming 25% of the maximum application rated of 6 pounds per acre) was incorrectly converted to the standard DFR units (16.8 µg/cm^2). This error led to a ten-fold underestimate of both field worker ADDs and had a similar effect on the MOEs. OEHHA recommends that the calculations of the DFR and ADDs be reviewed, and revised as necessary.

3. Residential Exposure

o   The AgDRIFT model was used to predict the magnitude of off-site spray drift deposition following ground boom applications. However, this model cannot generate airborne pesticide concentrations and therefore inhalation exposures of residential and occupational bystanders in this scenario were not assessed. This is important because over 70% of all propanil used in California during the years 2008-2012 was applied by ground equipment (DPR, 2016a). OEHHA recommends that the impact of this limitation of the AgDRIFT model and the lack of data to characterize inhalation exposure due to off-site spray drift be discussed.

o   Exposure to propanil in "take home" dust and ambient air was either not discussed (dust) or discussed but not included (ambient air) in the exposure assessment of residents and workers. The draft RCD claimed that these pathways are relatively unimportant. OEHHA recommends that the HEAD provide some data and maybe example calculations to support this claim.

4. Dietary Exposure Assessment

o   OEHHA agrees with the general approach taken in the dietary exposure assessment.

o   The percent of crop treated factor needs to be recalculated to include the acres of crop harvested and rounding as per DPR guidance.

o   The inclusion of non-consumers in the chronic dietary exposure assessment can lead to underestimation of consumers' exposures to 3,4-DCA via rice consumption. Rice is rarely if ever consumed by a significant proportion of individuals in California, though it is a daily staple of some ethnic groups. OEHHA recommends that DPR use consumer-only data to evaluate chronic exposure to 3,4-DCA in rice.

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III. RESPONSES TO CHARGE STATEMENTS

The responses to some of the charge statements are intended to be brief to avoid redundancy with the comments in Section II and the detailed discussion of OEHHA's comments in Section VI.

A. Hazard Identification and Risk Characterization

1. A lowest effective dose (LED1SD) equal to 14.2 mg/kg/day from a subchronic feeding study in rats that increased blood metHb levels at day 5 (O'Neill 2002) was selected as the acute no observed effect level (NOEL) for propanil.

OEHHA agrees with the selection of increased blood metHb levels from the O'Neill study (2002) as the critical endpoint for the acute exposure scenario. OEHHA also agrees with the use of a benchmark response of 1SD for that effect as it is unclear what percentage of increased blood metHb levels in the animal studies would be considered adverse.

2. A target margin of exposure (MOE) of 100 (10x UF for interspecies extrapolation and a 10x UF for intraspecies variability) was considered prudent for the protection of humans from propanil toxicity.

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, OEHHA recommends DPR increase the total intraspecies UF to 30 to protect sensitive populations, such as infants and small children from methemoglobinemia. This increase is from the use of OEHHA's default UF of 10 for intraspecies pharmacokinetic variability, which accounts for subpopulations (such as infants and elderly) possibly being more sensitive than the general population to the toxicity of a chemical. An intraspecies pharmacodynamic UF of 3 is appropriate.

3. Linear low-dose extrapolation was not used to evaluate propanil's putative oncogenicity.

DPR's rationale for this statement is that propanil is acting more likely as a tumor promotor based on the lack of evidence for genotoxicity, lack of clear dose-response, and the observation that tumors types observed were common in the animal bioassays. OEHHA disagrees with this statement (see the detailed

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comments in Section IV.F.). There is sufficient evidence of genotoxicity for propanil and 3,4-DCA. There are statistically significant positive dose-response relationships between propanil dose and tumor incidence for three tumor types in two animal species. Thus, OEHHA recommends using the default linear low-dose extrapolation to estimate cancer risk from lifetime exposure to propanil.

B. Worker and Bystander Exposure Assessment

1. **When propanil-specific dermal absorption studies are not available, dermal absorption is estimated using a default dermal absorption value according to DPR Human Health Assessment (HHA) Branch practice (see propanil EAD, Section IV-1).**

The draft propanil HEAD described the rationale for not estimating a dermal absorption rate by comparing the LOEL for the oral and dermal exposure routes. This method was used by US EPA (2006). Instead, DPR applied a default dermal absorption rate of 50% as directed by departmental policy (DPR, 1996). OEHHA agrees that this default absorption rate is health-protective. However, OEHHA recommends that the 1996 departmental policy memo on dermal absorption be included in the appendix and that DPR discuss the uncertainties in applying this policy.

2. **Because no exposure monitoring data were available, HHA used the PHED Database to estimate handler dermal and inhalation exposure (see propanil EAD, Section VI-1-1.1).**

OEHHA agrees that, in the absence of propanil-specific monitoring data, the use of PHED data to calculate a high-end occupational handler exposure estimate is appropriate. OEHHA recommends that DPR provide additional clarification on how adjustment factors for PPE were applied in calculating the dermal exposure estimates.

3. **When specific dislodgeable foliar residue (DFR) data are not available, the default DFR (25% of the maximum use rate) is used to estimate the field worker exposure based on U.S. EPA Policy (see propanil EAD, Section VI-1-1.2).**

DPR applied a default method to estimate DFR as recommended by the US EPA Science Advisory Council for Exposure policy (US EPA, 2017) because propanil-specific DFR data were not available. OEHHA agrees that this approach is reasonable. However, as noted in the Major Comments section, OEHHA found a mathematical error in the DFR calculation that needs to be corrected.

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4. HHA used computer modeling to estimate residential bystander exposure from spray drift (See propanil EAD, Appendix).

Dermal and incidental oral exposure estimates for all spray-drift-related scenarios were calculated using a multi-step approach (US EPA, 2012; US EPA, 2013). First, horizontal deposition of spray drift was estimated with either the AgDRIFT model (ground boom application) or AGDISP model (aerial application). Next, a turf transfer protocol was used to estimate potential exposure via dermal or oral routes. In general, OEHHA concurs with this approach. However, in the estimates of dermal exposure and incidental oral ingestion of residential bystanders following ground boom applications, OEHHA recommends that DPR provide additional clarification for the selection of the less conservative 50th percentile horizontal deposition output curve in AgDRIFT, as it differs from US EPA recommendations (US EPA, 2013).

For aerial applications, propanil concentrations in air were modelled and used to estimate the inhalation exposure of residential bystanders. Simulating different aircraft operating under standard conditions, with the AGDISP model, DPR predicted 1-hour time-weighted average air concentrations between the field edge and 1000 feet downwind. Choosing the highest predicted concentration at specific locations, DPR estimated inhalation exposure for children (ages 1-2 years) and adults using standard formulas. (See Tables 7 and 8 of Appendix A in the HEAD). OEHHA agrees with this approach as it assumes a worst-case estimate for each distance. However, the lack of inhalation exposure estimates for bystanders following ground boom applications may have led to an underestimation of aggregate exposure to residents.

AGDISP, which uses more refined and improved versions of the AgDRIFT aerial algorithms, was used to estimate horizontal deposition and air concentrations following aerial application (DPR, 2016a). Two key input parameters, spray quality (distribution of droplet sizes) and release height, were selected to exactly match current California regulatory requirements. OEHHA agrees that use of the AGDISP model for estimating exposure following aerial application is reasonable, but suggests that the exposure appraisal section of the HEAD include a brief discussion of whether this model has been validated for this purpose.

IV. DETAILED COMMENTS

A. Introduction

Propanil is a selective post-emergent general use herbicide registered to control broadleaf and grass weeds on rice fields (US EPA, 2003). It is typically applied as a broadcast treatment with ground boom sprayers and aerial equipment onto drained fields with young rice plants. There are no residential uses for propanil, but there is potential for workers or bystanders near application sites to be exposed through spray-drift.

Both mammals and plants metabolize propanil through either aryl acylamidase hydrolysis of the parent compound to 3,4-DCA (DPR, 2016a) or oxidation of the propyl moiety. Many toxic effects of propanil in mammals are mediated through 3,4-DCA. 3,4-DCA can be further metabolized by cytochrome P450s to generate other metabolites (e.g., OH-3,4-DCA) that are responsible for the oxidation of hemoglobin (Hb), and the formation of metHb. Known downstream effects of metHb noted in humans and in animals include methemoglobinemia, hemolytic anemia, and hemosiderosis of the spleen.

US EPA considers propanil to have "low acute toxicity" and "suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential" in their Registration Eligibility Decision (RED) (US EPA, 2003).

In the following sections, OEHHA provide a more detailed discussion of the major comments and answers to charge statements presented in Sections II and III, as well as some additional comments.

B. Pharmacokinetics

DPR evaluated propanil pharmacokinetics from six registrant-submitted animal studies as well as two human studies from the open literature.

Animal pharmacokinetic studies indicated that absorption via the oral route is rapid and expected to be 100%. Propanil is rapidly metabolized by acylamidase hydrolysis to 3,4-DCA, then further metabolized to a variety of secondary and tertiary metabolites prior to excretion. This is presented as Figure 2 in the draft RCD (Page 26). Two aspects to this figure that need clarification are:

1) The labeling of pathways A and B in Figure 2 did not appear to be consistent with the description in the text. On page 20, the text described Pathway A for oxidation to M* and Pathway B for aryl acylamidase mediated reaction with the formation of 3,4-DCA. The metabolic pathways shown in Figure 2 (page 26) is consistent with

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Propanil
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the description. However, it is the opposite on page 23, "…Pathway A is characterized by an aryl acylamidase-mediated hydrolysis step…while pathway B is characterized by a lack of the former." OEHHA recommends the text and/or figure labeling be corrected to reflect the correct metabolic pathways.

2) The discussion of N-OH-3,4-DCA as a primary metabolite and 3,4-DCA as a secondary metabolite on page 20 was misleading. It implied propanil is first metabolized to N-OH-3,4-DCA and then to 3,4-DCA. The arrows in Figure 2 depict the exact opposite – propanil is first metabolized to 3,4-DCA and then N-OH-3,4-DCA. This is consistent with the description on page 9, "Following the hydrolysis of the parent molecule's amide linkage, the primary amine of 3,4-DCA is susceptible to N-hydroxylation catalyzed by cytochrome P450. The resulting two metabolites are directly responsible for the oxidation of Hb to metHb: N-hydroxy-3,4-DCA (N-OH-3,4-DCA) and 3,4-dichloronitrosobenzene (DCNB)." The metabolic pathway of propanil is important because the information is critical to understand the chemical species that oxidize hemoglobin to metHb, the critical endpoint of acute and subchronic toxicities.

Human pharmacokinetic studies were limited to exposure to high doses, but provided useful information to show that 3,4-DCA can be formed in humans. Roberts et al. (2009) conducted a pharmacokinetic study on patients with hospital admissions related to acute, self-poisoning from propanil in Sri Lanka. The average elimination half-life of propanil in the blood of human was 3.2 hours. 3,4-DCA blood concentrations were both higher and more persistent than the parent compound. Another study by Pastorelli et al. (1998) measured 3,4-DCA in the blood and urine of 2 propanil exposed Italian workers. Authors found that 3,4-DCA-Hb was a sensitive biomarker of propanil exposure and the presence of 3,4-DCA-Hb showed the formation of 3,4-DCA in humans.

C. Non-cancer Toxicity Endpoint and Dose-Response Analysis

The draft RCD included a comprehensive description of the toxicological database for propanil, 3,4-DCA, and chemical contaminants of prepared propanil, 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB). The review of propanil was complete and the rationale for identifying the critical endpoints and PODs for non-cancer oral toxicity for various exposure durations were clearly stated.

OEHHA has two general comments regarding POD selection: (1) the use of propanil PODs for evaluating exposures to 3,4-DCA, and (2) BMR selection.

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1) The extractable species from plant material such as rice are mostly 3,4-DCA and its conjugates. However, the toxicity database of 3,4-DCA is not complete. DPR relied only on propanil toxicity data for evaluating health risks associated with rice and rice products consumption. DPR converted the residue levels of 3,4-DCA to propanil equivalents using the molecular weight ratio of these two compounds. The rationale was that the ratio of the oral LD_{50} values of propanil and 3,4-DCA (1.5-1.8) is similar to the ratio of the molecular weights of the two compounds (1.3). Thus, toxicities of the two compounds were considered equivalent on a per-mole basis.

OEHHA disagrees with this approach. It implies the relative toxicity potencies of propanil and 3,4-DCA derived from high dose mortality studies can be extrapolated, without adjustment, to much longer exposure durations and dose ranges that are relevant in environmental exposure. Comparing the NOELs from developmental toxicity and dermal toxicity studies for the two compounds, as shown in Table 1, does not support that toxicities are equivalent on a 'per-mole' basis and suggest that 3,4-DCA is more toxic than propanil in the animal studies.

The European Food Safety Authority (ESFA) determined that because the parent compound propanil is not present in plants, and the extractable residues contain mostly 3,4-DCA (free and conjugated), consumer risk assessment should refer to the toxicity of the 3,4-DCA metabolite (ESFA, 2011). OEHHA supports this conclusion and recommends that for this exposure scenario, the 3,4-DCA toxicity data at low doses should also be considered.

2) In the draft RCD, DPR assessed non-cancer toxicity endpoints by either using the BMD or the NOEL/LOEL approach. When the benchmark dose approach is used, DPR's defaults were a BMR of 1SD for continuous data and 10% for quantal data.

OEHHA agrees with the use of a BMR of 1SD for continuous data. It is unclear from the animal studies what observed changes in metHb levels would produce adverse clinical signs of toxicity. Using a BMR of 1SD in the absence of additional knowledge on biological significance of percentage change in that data set is consistent with the US EPA Benchmark Dose Technical Guidance (2012).

However, for quantal data, OEHHA typically uses a 5% BMR as the default for determination of the benchmark dose or concentration as the POD (OEHHA, 2008). OEHHA has shown that the lower 95% confidence bound on the BMC_{05} appears equivalent for risk assessment purposes to a NOAEL in well designed and conducted animal studies where a quantal measure of toxic response is reported. OEHHA recommends that for quantal data, a default BMR of 5% should be used.

Table 1. Comparison of toxicities of propanil and 3,4-DCA, based on animal studies.

Test type/species	Propanil[a]		3,4-DCA[a]	
	Dose	**Endpoint**	**Dose**	**Endpoint**
LD_{50} Oral, rat	779 to 1384 mg/kg (Table 5)	Mortality	530 to 880 mg/kg (Table 23)	Mortality
LD_{50} Dermal, rabbit	>2000 mg/kg (Table 5)	No signs of clinical toxicity or death	>631, but <1000 mg/kg (Table 23)	Mortality
LC_{50} inhalation, rat	>341 mg/kg (Table 5)	No mortality	101 to 528 mg/kg (Table 3)	Mortality
	NOEL	**Endpoint**	**NOEL**	**Endpoint**
Subchronic Dermal, 21-day, rabbit	1000 mg/kg[b] (Table 10)	No effects were observed at any dose	<60 mg/kg, only dose tested (Table 24)	Spleen enlarged and hemosiderosis
Subchronic Inhalation, 14-day, rat	No study available		2.4 mg/kg-day (Table 24)	↑ MetHb levels at 10.8 mg/kg-day
Developmental Toxicity Oral gavage, Gd 6 to 15, rat	Maternal= 20 mg/kg-day	No effect at the highest dose tested	Maternal= 5 mg/kg-day (Table 25)	↓body weight gain and food consumption at 25 mg/kg-day
	Developmental= 100 mg/kg-day	No effect at the highest dose tested	Reproductive/ developmental= 25 mg/kg-day (Table 25)	↑ post-implantation loss and delayed skeletal ossification at 125 mg/kg-day
	Study Type	**Result**	**Study Type**	**Result**
Genotoxicity	*In vitro* mutagenicity (bacteria and CHO cells), unscheduled DNA synthesis (rat hepatocytes, human fibroblasts)	Negative (12 studies) (Table 15)	*In vitro* mutagenicity (bacteria and CHO cells), unscheduled DNA synthesis (rat hepatocytes)	Negative (6 studies) (Table 26)
	In vitro mutagenicity in M45 strain (bacteria), and *in vivo* clastogenicity in *Drosophila* wing spot assay	Positive (2 studies) (Table 15)	*In vitro* clastogenicity in human lymphocytes, and Chinese hamster V79 cells	Positive (2 studies) (Table 26)

a/ Information and Tables refer to the draft RCD. Comparisons were made for the same species, except for genotoxicity studies.
b/ DPR considered the study unacceptable.
Abbreviations: Gd=gestational day, CHO=Chinese hamster ovary.

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Detailed discussions of critical studies, critical endpoints, and POD derivation for each exposure duration and route are provided below.

1. Acute Oral Toxicity Evaluation

DPR evaluated 10 toxicity studies in laboratory animals (acute toxicity studies as well as acute endpoints in subchronic/chronic, immunotoxicity, and developmental toxicity studies) which reported results for acute or short-term exposure (1-7 days) to assess acute oral risk to propanil. A summary of the acute NOEL and LOEL values for propanil from these studies was provided in Table 31 of the draft RCD (page 93-94; DPR, 2016a). The lowest NOELs derived from these studies were (1) decreases in body weight/body weight gain in rats following 7 days of dietary exposure from a chronic toxicity study (Bellringer, 1994) and (2) increases in metHb following 5 days of dietary exposure to propanil in a short-term feeding study in rats (O'Neill, 2002).

In Bellringer (1994), propanil was fed to 50 Crl:CD(SD)BR rats/sex/group at 0, 200, 600, and 1800 ppm for 104 weeks, corresponding to 0, 9, 27.7, and 88 mg/kg for males and 0, 11.5, 38.3, and 145 mg/kg-day for females. A satellite group of 20 animals/sex/dose received propanil for only 52 weeks for toxicity evaluation. The only acute effects measured in this study occurred after 7 days of treatment, were statistically significant, dose dependent decreases in body weight gain and food consumption in both males and females (Table 16, page 54; DPR, 2016a). These effects persisted throughout the duration of the study, but the decreases in body weight gain were the most pronounced during the first week, with females being more sensitive than males (gain was down to 2% compared to controls for males and -53% for females compared to controls, in the high dose group). The draft RCD calculated a $BMDL_{1SD}$ (referred to as the LED_{1SD} in the draft RCD) of 8.9 mg/kg-day in female rats for decreases in body weight gain from this study.

In O'Neill (2002), propanil was administered in the diet to 10 Crl:CD(SD)IGS BR rats/sex/group at 0, 300, 500, and 700 ppm, corresponding to 0, 25, 41, and 57 mg/kg-day for males and 0, 28, 41, and 67 mg/kg-day for females. The exposure was scheduled to last for 30 days, but was stopped on day 17 due to high levels of metHb. A dose-dependent increase in metHb was measured for both sexes following 5, 7, and 14 days of propanil treatment (Table 7, page 35; DPR, 2016a). On treatment day 5, metHb levels, expressed as percent of controls, were elevated to 167, 233, and 300% in males and to 217, 383, and 550% in females from the low to high doses. The draft RCD calculated a $BMDL_{1SD}$ of 14.2 mg/kg-day for elevated metHb in female rats from this study.

The draft RCD chose the $BMDL_{1SD}$ for increased metHb (14.2 mg/kg-day from O'Neill, 2002) as the acute POD, even though the acute $BMDL_{1SD}$ for body weight gain (8.9

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mg/kg-day from Bellringer, 1994) was the lowest value. The rationale provided were: increased metHb level was consistent with propanil mode of action (MOA), effect on metHb occurred as soon as one day following treatment but still persisted over studies of longer duration, data were amenable to modeling, and the POD was likely protective of other acute effects. DPR stated, "While decreased BW and BWG are supported by the data and regarded as indicators of general health, the corresponding mode of action is not understood."

OEHHA agrees with the selection of this critical endpoint. OEHHA recognizes that increased metHb is an important health effect associated with exposure to propanil. Increases in metHb levels were noted in virtually all animal studies in which propanil was tested, in all species, and preceded more severe effects such as methemoglobinemia and hemolytic anemia in studies of longer duration. Furthermore, this effect also occurred in humans exposed to propanil and is thus a relevant endpoint for risk characterization. However, the justification for not choosing body weight gain as the acute oral POD should be revised. It is often not necessary to understand the MOA of an adverse effect before it can be identified as the critical endpoint. The determination that an effect is treatment-related and considered adverse is sufficient justification. Decrease in body weight gain is a well-recognized systemic toxicity effect; it is used as an indicator of toxicity for the determination of maximally tolerated dose. Furthermore, effects on body weight and body weight gain were also observed in non-dietary studies, indicating these effects could not be attributed to diet palatability issues.

2. Subchronic Oral Toxicity Evaluation

DPR evaluated 12 oral studies with subchronic endpoints (1-13 weeks) in mice, rats, and dogs) to assess subchronic oral toxicity to propanil. A summary of the subchronic NOEL and LOEL values for propanil from these studies was provided in Table 32 of the draft RCD (page 97-99; DPR, 2016a). The draft RCD identified increased metHb as the critical endpoint and the two lowest BMDLs were 3 mg/kg-day from the 13 week dietary mouse study (Tompkins, 1993) and 5 mg/kg-day from the 13 week endpoint from the two-year chronic dietary rat study (Bellringer, 1994).

In Tompkins (1993), technical grade propanil was administered in the diet for 13 weeks to COBS-CD1 mice (10/sex/group) at 0, 400, 650, 900, and 1150 ppm. This corresponded to 0, 71, 120, 166, and 200 mg/kg-day for males and 0, 98, 155, 238, and 266 mg/kg-day for females, respectively. MetHb was elevated in both sexes in all treatment groups. Males also had a dose dependent decrease in Hb, statistically significant at the high dose. Splenic toxicity was also apparent as increased absolute and relative spleen weights, and increased hemosiderin (statistically significant at 900 ppm) were reported. There was no NOEL for this study and the LOEL was 71 mg/kg-

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day for the males and 98 mg/kg-day for the females. DPR calculated a $BMDL_{1SD}$ of 3 mg/kg-day for increased metHb levels in male mice.

Bellringer (1994) was described above under the acute oral exposure (Section III.C.1). The endpoint chosen for the subchronic oral exposure, however, was increased metHb in the satellite group (n=20) from the 13 week assessment. There was a dose dependent increase in metHb in all treated groups for both sexes, statistically significant for males in the mid and high dose groups (131% and 184% relative to controls, respectively) and statistically significant for females in all treated dose groups, 134%, 164%, and 207% relative to controls, at the low, mid, and high doses, respectively). The LOEL was estimated to be 14 mg/kg-day in the females (Table 16; DPR, 2016a). DPR calculated a $BMDL_{1SD}$ of 5 mg/kg-day for increased metHb in female rats.

The draft RCD selected 5 mg/kg-day, instead of the lower value of 3 mg/kg-day, as the critical POD for assessing subchronic oral exposure to propanil. The rationale was that the POD was similar in magnitude to the LOEL (14 mg/kg-day) and its identification is less dependent on model selection. The draft RCD determined that this critical POD is likely protective of systemic (including hematologic), developmental, and immunotoxic effects of propanil. OEHHA agrees with the chosen subchronic POD.

3. Chronic Oral Toxicity Evaluation

DPR evaluated chronic toxicity endpoints in five dietary exposure studies for propanil: mouse (2 studies), rat (1 study), and dog (2 studies). A summary of the NOEL and LOEL values was presented in Table 33 of the draft RCD (page 102-104; DPR, 2016a).

The lowest chronic POD came from the two year chronic rat study (Bellringer, 1994), briefly described in the acute oral exposure (Section III.C.1, above). Aside from the hematological effects (increases in metHb), chronic propanil exposure caused toxicity to the liver (including inflammation and hyperplasia of the bile ducts; hepatocellular adenomas in females), spleen (splenic enlargement and hemosiderosis), kidneys, and testes (increased relative organ weight characterized by interstitial cell hyperplasia, effects on total spermatozoa, and benign interstitial cell tumors) in the rat. A table of the effects reported from the study and the statistical analysis was presented in Table 16 (page 54-56) of the draft RCD. DPR modeled endpoints using a BMR of 10% or 1SD, and the results were listed in Table 33 (page 102-104). It should be noted that Table 33 (page 102) was incorrectly labeled for spleen hemosiderosis; the "Toxic effects at LOEL" was labeled as "Toxicity to spleen: ↑ hemosiderosis (Total) (m)" when the NOEL was calculated for week 104 males.

The lowest $BMDL_{10}$ from the Bellringer study (1994) was 0.5 mg/kg-day for splenic hemosiderosis in male rats at week 104 and it was determined to be the POD for

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chronic oral exposure. The rationale for this POD selection was that (a) Bellringer (1994) was a well-conducted study, (b) spleen toxicity was consistent with the MOA of propanil and the effect was reported in the other chronic toxicity studies, and (c) the POD was the lowest $BMDL_{10}$ derived and would be protective of other systemic effects of propanil.

OEHHA has several concerns regarding the POD and the endpoint selected:

1) The BMD modeling was based on the male rats alive at the study termination (week 104). High mortality was reported in the control and all the dosed groups (survivals at 104 weeks were 15/50 for the control and 17/50, 23/50, and 31/50 for the low-, mid-, and high-dose groups, respectively) and it could have an impact on the male splenic hemosiderosis results as well as the modeled dose-response curve.

2) The draft RCD presented only total incidence including all severities of hemosiderosis, a combination of trace, minimal, moderate, and severe effects. Because hemosiderosis is known to increase with age of the animal, the lowest severity of hemosiderosis may not be treatment related, especially for the 104-week data set consisting of the surviving and oldest animals in the study.

3) It is not clear if the reported total hemosiderosis incidence was treatment-related. While the rates were relatively low for the control males (27% and 22% of the surviving and the total number of animals, respectively, at 104 weeks), they were extremely high for the control females (100% and 96% of the surviving and the total number of animals, respectively, at 104 weeks).

OEHHA recommends a re-analysis of the hemosiderosis data based on when the endpoint was first observed, and take into consideration severity of this effect. As an alternative, OEHHA also recommends DPR consider "total pericholangitis" in the liver for males from the same study as the critical effect. The data for this endpoint demonstrated statistically significant, dose-responsive increases in both males and females, and was supportive of other liver effects measured in the same study, as well as other chronic studies in the database (Table 16, page 55; DPR, 2016a). This data is also amenable to BMD modeling and an appropriate BMR should be selected.

4. Inhalation Toxicity Evaluation

The inhalation toxicity database was limited and the only inhalation study available was an acute LC_{50} study (Durando, 2010a) with the highest dose of 341 mg/kg-day with no mortality reported. This study result was not appropriate for characterizing inhalation

risk. Due to the lack of appropriate inhalation toxicity data of propanil, DPR used oral PODs for route-to-route extrapolation and assumed 100% absorption in the lung.

OEHHA agrees with this approach and the assumption used. However, there is a concern on how the first-pass effect might influence the route-to-route extrapolation. When propanil is ingested, it first goes to the liver where most of the metabolism takes place and the resulting metabolites (i.e., 3,4-DCA) enter the blood stream and distributed to other body organs and tissues. In comparison, there is no pharmacokinetic data on propanil after inhalation exposure. The lack of a suitable inhalation study and the difference in pharmacokinetics of oral and inhalation routes may increase the uncertainty of assessing the health impact of inhalation exposure.

However, a 14-day inhalation study of 3,4-DCA (cited as Kinney, 1986 from ECB, 2006 in the draft RCD) had a stated NOEL of 2.4 mg/kg-day for increased metHb, which is lower than the acute oral POD (14.2 mg/kg-day) and subchronic oral POD (5.0 mg/kg-day) for the same endpoint. OEHHA suggests that DPR obtain this study, if possible, and evaluate it to see if it would provide information about the non-lethal inhalation toxicity of propanil. In addition, this study could potentially be used to derive a surrogate POD for the inhalation toxicity of propanil.

5. Dermal Toxicity Evaluation

The toxicity database for propanil dermal exposure included dermal LD_{50} studies (Table 31, page 94; DPR, 2016a) in rats (Durando, 2010b) and rabbits (Naas, 1989) where no mortality was observed, and one 21-day dermal study in rabbits (5/sex/dose) where no effects were observed at 0, 250, and 1000 mg/kg-day (Dykstra and Gardner, 1991) (Table 32, page 99; DPR, 2016a). This study was considered unacceptable because of deficiencies in the description of the experimental protocol.

Due to the lack of appropriate acute and subchronic dermal toxicity data of propanil, DPR used oral acute and subchronic PODs for route-to-route extrapolation. DPR also assumed 50% of the chemical applied dermally is absorbed. We agree with the use of this approach and the assumption.

D. Reproductive and Developmental Toxicity

The database of registrant-submitted reproductive toxicity studies of propanil included a two-generation and a three-generation dietary studies in rats. The details of these studies were well described and study summaries were presented in Table 12 of the draft RCD (page 45; DPR, 2016a). No parental systemic, reproductive, and pup effects were reported at the highest dose of 50 mg/kg-day by the three-generation dietary study.

Evidence of reproductive and developmental effects of propanil were reported in the two-generation dietary study (Stump, 1998), where rats were fed propanil at 0, 4, 11, or 43 mg/kg-day for males and 0, 5, 13, or 51 mg/kg-day for females. Reproductive effects in the parental generations only occurred at the high dose and included effects on reproductive organ weights (ovaries, testes, adrenals, prostate, seminal vesicles and coagulating gland, and the left epididymis), reduced epididymal and testicular sperm numbers, decreased sperm production rates, and reduced primordial follicles and corpora lutea in the high dose females. These effects are consistent with findings in the two-year chronic dietary rat study (Bellringer, 1994), which observed increased relative testes weights at similar doses and toxicity to the seminal vesicles and epididymis at approximately 20 mg/kg-day. Pups from this two-generation study (Stump, 1998) also experienced significant reductions in body weight; liver, testes, and adrenal weights, as well as delayed vaginal perforation in females and delayed balanopreputial separation in males at the high dose. The NOELs for parental systemic, reproductive, and pup effects from this study were 11 and 13 mg/kg-day for males and females, respectively.

The developmental toxicity study database, as summarized in the RCD, included one rat and one rabbit oral gavage studies. The summaries of these studies were presented in Table 14 of the draft RCD (page 47; DPR, 2016a). No adverse developmental toxicity was reported at the highest dose tested (100 mg/kg-day) in rats.

In rabbits, maternal reduction in average body weight and mortality were reported at the highest dose of 100 mg/kg-day. Total resorption was found only in rabbits that died at this dose. The draft RCD established a maternal NOEL of 20 mg/kg-day and a developmental NOEL at 100 mg/kg-day.

OEHHA agrees with DPR's conclusion that the lower PODs for metHb (in acute and subchronic exposures) would be protective of the reproductive and developmental effects of propanil.

E. Immunotoxicity

The draft RCD discussed one registrant-submitted immunotoxicity study, which showed suggestive evidence for immunotoxicity (Padgett, 2007). In this guideline study, there was an increased spleen primary IgM antibody-forming cell response in high dose males and all treated females, but none of the effects was statistically significant. Other splenic effects observed (i.e. increased relative spleen weight in high dose groups) were consistent with metHb formation and the known propanil mode of action. A few immunotoxicity open literature publications were cited in the draft RCD, but no study descriptions or summaries of their findings were provided. The draft RCD stated that

the critical animal PODs chosen were protective of immunotoxic effects observed in the animal studies.

OEHHA suggests a more comprehensive review of immunotoxicity to include the open literature and reevaluate the statement the PODs chosen are protective of potential immunotoxicity in humans. There are several publications on the potential immunotoxicity of propanil in humans and animals (Corsini et al., 2007; Hansen et al., 2010; Lewis et al., 2013; Salazar et al., 2008). Propanil has been found to cause diverse effects on both the innate and adaptive immune responses (reviewed in Salazar et al., 2008). Furthermore, a human study showed propanil effects on immune responses in agricultural workers following intermittent occupational exposures (Corsini et al., 2007). While the immunomodulatory effects of propanil reported in this study were mild (increased plasma IgG_1, LPS-induced IL-6 release, and a reduction in PHA-induced IL-10 and IFN release), these effects were measured in workers and at occupational exposure levels with few other reported adverse health effects (two workers with the highest urinary 3,4-DCA levels complained of headache). Furthermore, additional evidence of immunotoxicity also exists in several guideline toxicity studies. Changes in splenic weights in chronic feeding studies in rats (Bellringer, 1994; Tompkins, 1993; Tompkins, 1994) could indicate toxicity to secondary immune organs; these should be included in the overall evaluation of immunotoxicity.

F. Carcinogenicity Weight of Evidence

In the draft RCD, DPR did not derive a cancer potency to evaluate lifetime exposure cancer risk, citing a lack of evidence for genotoxicity and dose-responsiveness of tumor formation. They also suggested that propanil only acts as a tumor promotor, in part due to commonality of the tumors detected and significant increase in tumors mainly at the high dose. OEHHA disagrees with these conclusions.

1. Genotoxicity

The draft RCD noted that there was a limited evidence for genotoxicity of propanil because positive results were only found in one of 11 *in vitro* mutagenicity studies and one of three *in vivo* clastogenicity studies (DNA damage in *Bacillus subtilis* and somatic mutation and combination in *Drosophila melanogaster* larvae, page 47 and Table 15 in DPR, 2016a). In the "Weight of the Evidence" discussion, the draft RCD stated that there was "Lack of evidence for genotoxicity" for propanil (page 105; DPR, 2016a). However, the genotoxicity of 3,4-DCA, while considered genotoxic in the draft RCD, was apparently excluded from the weight of evidence consideration.

In addition to studies presented in the draft RCD, there are two additional publications that showed genotoxicity of 3,4-DCA. Eissa et al. (2012) reported chromosomal

aberrations in both bone marrow cells and spermatocytes in mice exposed to 3,4-DCA. In this study, 20 male Swiss Albino mice per dose were treated by gavage with 0, 13.83, 27.67, or 55.33 mg/kg-day of 3,4-DCA for 30 consecutive days. 3,4-DCA induced a significant dose-dependent decrease in mitotic index in both bone marrow cells and spermatocytes. There was also a dose-dependent increase in structural abnormalities and total chromosomal aberrations in bone marrow cells, significant at all dose levels, up to an almost 400% increase over the dose range. Similar results were observed in spermatocytes and the induction was even greater, with over an approximately 800% increase.

Osano et al. (2002) conducted an *in vitro* genotoxicity test, the Mutatox® assay, with a dark mutant of *Vibro fischeri*, a marine photobacterium. This test indicated that 3,4-DCA was genotoxic at all concentrations tested, in levels as low as 0.10 µM. The Mutatox® test is sensitive and responsive to chemicals that are DNA damaging agents, DNA intercalating agents, DNA synthesis inhibitors, and direct mutagens (Kwan et al., 1990). Details of the positive genotoxicity study results for propanil and 3,4-DCA are provided in Table 2 below.

It is OEHHA's opinion that 3,4-DCA should also be included in the weight of evidence for the determination of carcinogenicity of propanil. First, 3,4-DCA is a key metabolite of propanil in humans (Roberts et al., 2009). Second, humans are also directly exposed to 3,4-DCA through rice consumption. Third, there is strong evidence for the genotoxic potential of 3,4-DCA, from both in vitro and in vivo studies (see Table 2 of this report).

Table 2. Positive genotoxicity studies for propanil and 3,4-DCA.

Assay end point	Test systems	Dose levels	Results -S9	Results +S9	Reference
Propanil					
In vitro Mutagenicity, (Recombin-ation)	*Bacillus subtilis* (H17 and M45)	0.1 to 1000 µg/plate	Positive for M45	Negative	Simmon, 1979 (FIFRA guideline study, unacceptable by DPR- report lacks sufficient detail)
In vivo Clastogenicity, (Wing spot test)	*Drosophila melanogaster* larvae	0.1, 0.5, 1, 2, 5, and 10 mM	Positive	NA	Kaya et al., 2000
3,4-DCA					
In vitro Clastogenicity (CA and SCE)	Human lymphocytes	0 to 1 mM	Positive	Positive	Bauchinger et al., 1989
In vitro Clastogenicity (Mitotic spindle disruption)	Chinese hamster V79 cells	0 to 1 mM	Positive	NA	Bauchinger et al., 1989; Salassidis and Bauchinger, 1990
In vivo Clastogenicity (CA and mitotic index)	Swiss Albino mice gavage for 30 days	0, 13.83, 27.67, 55.33 mg/kg-day	Positive for CA and ↓ MI in bone marrow cells and spermatocytes	NA	[a]Eissa et al., 2012
In vitro Genotoxicity test with Mutatox®	*Vibrio fischeri* (biolumin-escent marine bacterium)	10 to 108.95 µM	Positive at all concentrations tested	Negative	[a]Osano et al., 2002

a/ Not included in the draft RCD.
Abbreviations: CA=chromosomal aberration, FIFRA=Federal Insecticide Fungicide and Rodenticide Act, MI=mitotic index, NA=not applicable, S9=liver metabolic activation fraction, SCE=sister chromatid exchange.

2. Experimental Animal Evidence

The draft RCD reported tumor findings in four FIFRA guideline acceptable studies: benign testicular interstitial tumors in male rats (Bellringer, 1994; Table 16, page 56), hepatocellular adenoma in female rats (Bellringer, 1994, Table 16, page 56) and male mice (Tompkins, 1994; Table 17, page 59), and malignant lymphoma in female mice (Tompkins, 1994; Table 17, page 59). These studies are well described in the draft RCD and OEHHA agrees with the approach to determine tumor incidences using animals "at-risk."

However, OEHHA has some concerns about the quantitative analysis of the data.

1) For all tumor sites, DPR concluded that there was a lack of dose-response based on a lack of statistical significance by pair-wise comparison in the mid-dose groups (note that the draft RCD referred to this term as "group-wise" comparison) and dismissed the tumor findings for quantitative assessment because they were observed mainly at the highest dose tested.

In OEHHA's opinion, these determinations are inconsistent with the US EPA cancer risk assessment guidance, as well as with those from other agencies such as the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) (US EPA, 2005; NTP, 2015; IARC, 2006). The US EPA Guidance states that the tumor incidence data are considered significant and treatment-related based on *either* trend or pair-wise comparison (when $p < 0.05$). Furthermore, it states, "The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms). The purpose of two or more lower doses is to provide some information on the shape of the dose-response curve." Thus, lack of statistical significance by pair-wise comparison in the lower doses does not exclude the consideration of these data in an overall evaluation. Both the NTP and IARC also support statistical analysis of trend (NTP, 2015; IARC, 2006). OEHHA subjected these tumor datasets to trend tests and found all four were statistically significant by Cochran-Armitage test for trend (Table 3). OEHHA recommends DPR include tests for trend for neoplastic effects in the chronic toxicity studies.

2) DPR did not calculate a cancer slope factor. The rationale was that tumors found were common tumors found in aging rats and mice (page 4; DPR, 2016a) and occurred only at high doses. For the statistically significant interstitial cell tumors of the testis in male rats, the draft RCD stated, "lack of evidence for genotoxicity and lack of group-wise significance for all but the high dose preclude the calculation of a linear slope factor…" (page 105; DPR, 2016a). A similar argument was made in the draft RCD regarding hepatocellular adenomas found in male mice and malignant lymphoma in female mice from the chronic mouse study (Tompkins, 1994). DPR stated, "The lack of a clear dose response in the mid-dose group for either tumor in the mouse ruled out the calculation of slope factors to calculate the long-term oncogenic risk from exposure to propanil for this end-point" (page 106; DPR, 2016a).

Table 3. Estimation of animal cancer slope factors from the cancer bioassay data of propanil.

Study duration and route	Species and sex	Tumor type (week first tumor detected)	Dose (mg/kg-day) Incidences				Animal CSF[a] (mg/kg-day)$^{-1}$	Study
2-Year dietary	Male CD rats	Testes-Benign interstitial cell tumor (week 86)	0	9	28	88	0.009	Bellringer 1994
			3/39***	3/34	8/40	29/40***		
2-Year dietary	Female CD rats	Hepatocellular adenoma (week 79)	0	12	38	145	0.001	Bellringer 1994
			1/37**	0/40	1/41	6/47		
2-Year dietary	Male CD-1 mice	Hepatocellular adenoma (week 67)	0	75	150		0.001	Tompkins 1994
			1/47**	3/52	8/51*			
2-Year dietary	Female CD-1 mice	Malignant lymphoma (week 33)	0	89	174		0.001	Tompkins 1994
			3/59**	4/58	12/58*			

a/ OEHHA calculated. Second degree multistage cancer model was used for the analyses. Statistical significance by Cochran-Armitage test for trend (indicated on control group) or Fisher Exact test for pair-wise comparison (indicated on significant dose group when compared to control): Statistically significance at * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

OEHHA disagrees with the rationale. Cancer potencies are often estimated for common tumors when they are treatment-related. In the propanil database, three tumor types were reported in four studies and all the incidences were statistically significant for trend, had a clear dose-dependent increase in tumor formation, and benign interstitial cell tumors in the testes of rats were highly statistically significant by pair-wise comparison at the high dose group (Table 3). Furthermore, the first malignant lymphoma was found at 33 weeks in female mice and the first hepatocellular adenoma was found at 67 weeks in male mice, these are early tumors and thus not arising simply due to old age.

In order to understand DPR's determination of lack of dose-response relationship for the tumors, OEHHA conducted a quantitative analysis of the data provided in the draft RCD. OEHHA used the second degree multistage model in the BMD software to model these datasets and estimated animal cancer slope factor ranged from 0.001 to 0.009 (mg/kg-day)$^{-1}$ (Table 3).

Overall, OEHHA determines there is sufficient evidence for carcinogenicity of propanil and the derivation of a slope factor. The rationale in the Draft RCD for not deriving a

slope factor was not supported by data. Thus, OEHHA recommends a quantitative risk assessment be conducted using the default non-threshold approach (low-dose linear extrapolation) to evaluate the cancer risk from lifetime exposure to propanil.

G. Uncertainty Factors

1. Interspecies Extrapolation

OEHHA supports DPR's use of an interspecies UF of 10 because all PODs were derived from laboratory animal studies.

2. Intraspecies Extrapolation

In the draft RCD, a default intraspecies UF of 10-fold was applied to account for the pharmacokinetic and pharmacodynamics differences within the human population. It is OEHHA's opinion that an intraspecies UF of 10 is insufficient. Thus, OEHHA recommends an intraspecies UF of 30. The larger UF is particularly needed when the critical effect is metHb formation.

For non-cancer effects, OEHHA's view is that there are many factors affecting human variability in response to a chemical exposure (OEHHA, 2008; Zeise et al. 2013). The scientific basis for this recommendation is detailed in OEHHA's peer reviewed Air Toxics Hot Spots Risk Assessment Guidelines, Technical Support Document for the Derivation of Reference Exposure Levels (OEHHA, 2008). Based on analyses of human pharmacokinetic variability, OEHHA's practice is to increase the traditional intraspecies pharmacokinetic UF of √10 to 10. This increase would account for the wide variability in pharmacokinetics in the population, especially among subpopulations such as infants and children, pregnant women, and the elderly. For example, elderly people have more fluctuating Hb levels and is more susceptible to the effect of metHb formation. Furthermore, some individuals are more susceptible to methemoglobinemia due to a cytochrome b5 reductase deficiency or glucose-6 dehydrogenase deficiency (reviewed in Blom, 2001).

More importantly, infants and young children were estimated to have higher dietary exposures to propanil equivalents than for adults, in term of µg/kg-day (Table 42, page 117; DPR, 2016a). Infants are also more sensitive to metHb-generating chemicals than adults, as they have reduced levels of nicotine adenine dinucleotide (NADH, the cofactor (electron donor) for metHb reductase), higher concentration of fetal hemoglobin in their erythrocytes (fetal hemoglobin is more susceptible to oxidation than adult hemoglobin), and increased tendency for Heinz body formation in the presence of oxidant compounds (Seger 1992; cited in National Academy of Sciences, NAS, 2000; Ohls, 2011). Increased susceptibility to chemical induced methemoglobinemia has

been demonstrated for dapsone in both older children and neonates (Wright et al., 1999; Kabra et al., 1998).

H. Exposure Assessment

For this review, OEHHA summarized the source of the propanil levels in Table 4. It would be helpful to have such a table in the draft RCD since the information is in various sections in the document. The table shows that propanil levels for worker and bystander inhalation and dermal exposures were modeled, while propanil and 3,4-DCA levels in rice and water were measured.

1. Physical and Chemical Properties, and Environmental Fate

Workers and residents may be exposed to propanil via aerosol spray drift. The very low volatility of this pesticide would prevent any significant post-application exposure due to re-volatilization (Richards et al, 2001; Kanawi et al., 2016). OEHHA suggests that DPR cite the draft 2014 US EPA volatilization screening analysis that supports this conclusion (US EPA, 2014a).

Registrant studies conducted in Arkansas and Louisiana showed that propanil is found in the water or soil of rice paddies for no more than a few days post-application. A key degradation product of propanil, 3,4-DCA, had a long half-life of 9.5-11.6 days in soil and 2-3 days in water samples from rice paddies (Propanil Task Force, 1992a and 1992b). These data are likely relevant in assessing the effect of the mandated seven-day holding time for field drainage water on propanil and 3,4-DCA concentrations in surface and drinking water (see additional comments in the following section).

Recently, Kanawi et al. (2016) reviewed the environmental fate of propanil and concluded that while ground water had been contaminated at sites used frequently for mixing and loading activities, modelling studies suggested "propanil does not enter groundwater in areas with heavy clay, clay loam soils with poor infiltration." California drinking water monitoring studies showed that propanil and 3,4-DCA residue levels were higher in surface water compared to ground water (DPR, 2016a, Table 37), so OEHHA concurs with the use of the DPR surface water monitoring database (DPR, 2016b) to provide high-end estimates of propanil and 3,4-DCA concentrations in drinking water.

Table 4. Chemical species in environmental media and how the levels were estimated.

Exposure Groups	Application Types/ Sources	Inhalation Exposure	Dermal Exposure	Oral Incidental Ingestion[a] or Dietary Exposure
Handlers	All types	Propanil from PHED	Propanil from PHED	NA
Rice field workers	All types	NA	Propanil from application rate	NA
Residential bystanders	Groundboom	NA	Propanil by AgDRIFT	Incidental ingestion by child only:
	Aerial	Propanil by AGDISP	Propanil by AGDISP	Propanil by AgDRIFT or AGDISP
General population	Food	NA	NA	3,4-DCA measured in rice from field trials
	Water	NA	NA	Propanil and 3,4 measured in surface water samples

a) Incidental oral ingestion includes hand-to-mouth, object-to-mouth, and soil ingestion.
Abbreviation: NA= not applicable or not estimated.

2. Pesticide Use and Application

In California, propanil is only approved for use on rice crops, which are grown primarily in the Sacramento Valley (CDFA, 2013). At an early stage of rice growth, the field is drained, and the exposed vegetation treated with propanil and other herbicides. After a limited period of sunlight (~ 8 hours), the field is re-flooded (DPR, 2016a; UCCE, 2015). Mitigation practices noted in the amended EPA RED (US EPA, 2006) state that, in general, flood water must be held for 7 days after application. OEHHA suggests that the draft RCD include a brief discussion of this practice, assess the extent to which it reduces surface water contamination, and determine what impact it might have in reducing exposure via ingestion of drinking water.

Data reported by DPR indicate that propanil was the 15th most applied pesticide in California, with almost 2 million pounds applied in 2014 (DPR, 2016c). The most recent usage data presented in the draft RCD (Table 3) was from 2010. OEHHA suggests this table be updated to include the 2014 data.

3. Reported Illness

In California, only one reported case of pesticide illness that involved propanil has been observed since 1992. However, SENSOR-Pesticides, a multi-state pesticide illness reporting system, identified 10 cases in other states that involved propanil and bystanders affected by off-target drift (US EPA, 2015). OEHHA recommends that the

draft HEAD include these illness cases as they suggest the need to evaluate residents' potential exposure to propanil as a result of spray drift.

4. Dermal and Inhalation Absorption Factors

No studies of propanil dermal absorption rate (DAR) were available. Instead, a dermal absorption default value of 50% was used to estimate dermal propanil exposure in this risk assessment (DPR, 1996). This default value is 2.5-fold higher than that used by US EPA (USEPA, 2006). OEHHA agrees that use of this default absorption rate is reasonable and health protective.

No inhalation absorption rate (IAR) studies were available and a default IAR of 100% was used to estimate propanil inhalation exposure. OEHHA agrees with the use of this assumption.

5. Occupational Exposure

In the calculation of an acute ADD for the aerial applicator (enclosed cockpit), an additional protection factor ("with gloves") might have been mistakenly applied (Table 6, row 11, column 5). The applicator in the enclosed cockpit is not required to wear gloves. The acute ADD calculated by OEHHA was >3-fold higher than the value reported in the draft HEAD. OEHHA recommends that DPR check the calculations of this exposure scenario.

For the other occupational handler scenarios, OEHHA calculates exposure estimates by following DPR guidance documents and additional details provided within the draft HEAD, but we cannot replicate the dermal mean estimates reported in Table 5 (column 6) of the draft HEAD (DPR, 2007a; DPR, 2007b; DPR, 2016a). OEHHA recommends that DPR include additional detail or sample calculations to clarify how the reported dermal mean estimates were calculated.

For the occupational post-application exposure estimate for field workers (DPR, 2016a), there appears to be a significant error in the conversion from application rate to DFR units in Table 7. According to the current US EPA guidance (US EPA, 2017), the calculated default DFR (25% of the application rate) at day 0 should have been 16.8 $\mu g/cm^2$ and not 1.5 $\mu g/cm^2$. Consequently, all of the field worker exposure estimates should be approximately ten-fold higher than those reported in the draft HEAD (Tables 7 and 8), and the related aggregated exposure estimates and the MOEs would also be affected.

Apart from this numerical mistake, OEHHA agrees that application of this methodology to calculate the default DFR was appropriate given the lack of propanil-specific DFR data.

It is not clear in the text or Table 7 of the draft HEAD what assumptions, such as a default dissipation rate, were applied in estimating the DFR at the Restricted Entry Interval of one day post-application. OEHHA recommends that additional details and a sample calculation be provided.

6. Residential Exposure

In estimating human exposure, DPR used the AgDRIFT model to estimate horizontal deposition for ground application of propanil, but applied the AGDISP model to estimate both horizontal deposition and air concentrations near aerial application sites. These approximations were then used to estimate dermal and incidental oral exposure for young children (ages 1 to < 2 years) and adults by applying Standard Operating Procedures for estimating the transfer of pesticides from turf (US EPA, 2013; US EPA, 2014b). OEHHA agrees with this approach.

All dermal and oral exposure estimates for the ground boom exposure scenarios were based on screening level horizontal deposition estimates generated by the AgDRIFT model and included two refined input parameters. California regulations require the use of "very coarse to extra coarse" spray quality (droplet size distribution) for propanil applications. However, the AgDRIFT model does not provide a comparable droplet size setting. Consequently, DPR used the largest droplet size possible to estimate ground boom deposition. This predicts a wider horizontal deposition than would actually occur if a larger droplet size setting were available. Therefore, the range of deposition may have been overestimated while the deposition of propanil onto soil may have been underestimated. OEHHA recommends that DPR discuss the relationship between dispersion distance and the magnitude of surface deposition onto soil, and how this interaction may have affected the dermal and oral exposure estimates.

"Take-home" dust as a potential source of propanil exposure for residents nearby agricultural operations was not mentioned in the exposure assessment. One study found detectable amounts of propanil in three of eight residences near treated rice paddies (Richards et al., 2001). Refer to OEHHA's recommendation in the Major Comments section of this document.

Lastly, propanil was detected in 24-hour ambient air samples (range: < 0.004 to 0.149 $\mu g/m^3$; average air concentration for all samples ± standard deviation: 0.033 ± 0.029 $\mu g/m^3$) collected over an 8 week period of peak seasonal propanil use at air monitoring stations in high-use areas of Butte, Glenn and Colusa counties (ARB, 2009). The

significance of inhalation exposure to propanil in ambient air relative to the other pathways that were evaluated in the draft RCD and draft HEAD needs to be discussed.

I.   Dietary Exposure Assessment

The draft RCD estimated the acute and chronic exposures from food and drinking water. The residue values were propanil equivalents (propanil and its metabolites convertible to 3,4-DCA) from rice field trial data and DPR surface water monitoring data. Exposure doses were calculated using the Dietary Exposure Evaluation Model software (DEEM) which incorporates National Health and Nutrition Examination Survey (NHANES) two-day food consumption data for 2003 through 2008. A percent crop treated factor of 66% was applied to rice residues for calculating chronic exposure dose. OEHHA agrees with the general approach. Specific comments are presented below.

1. Residue Data

DPR uses the percent crop treated (PCT) to calculate chronic exposure dose from food. PCT is defined as the number of acres treated divided by the number of acres harvested. DPR used the following equation to calculate PCTs:

Percent Crop Treated (PCT)(%) = (Applied (lbs. AI)/(Seasonal Maximum Application Rate (8 lbs AI)/A Treated) x 100%

The above equation does not include the number of acres harvested and thus does not estimate PCT. OEHHA recommends that the RCD calculate PCT using "acres harvested." Alternatively, the US EPA PCT value can be used and uncertainties with its use for California specific exposure estimates be discussed. In addition, DPR's Guidance for Dietary Exposure Assessment (DPR, 2009) states that "... DPR default procedure is to select the highest PCT from available data, and to round this value to the next highest multiple of five." The guidance for calculation of propanil PCT was apparently not applied.

2. Exposure Calculation using DEEM-FCID

For chronic exposure assessment, DPR used DEEM per capita consumption in which the amount that an individual consumes is combined with the zero consumption of those who do not consume. When a significant proportion of the population never or almost never consumes a certain commodity over the long term, the mean per capita consumption rate underestimates the mean consumer-only consumption rate. For rice, the only commodity to which propanil is applied in California. The NHANES data on eating patterns over one year suggest that a substantial proportion of the population (18.5%) never or almost never consumes rice over the long term. Thus, OEHHA

recommends that DPR consider using consumer-only data to derive chronic exposure dose estimates for this pathway.

One of the population subgroups assessed was noted as "pregnancy/lactation." OEHHA suggests that the term be changed to "women of reproductive age" or to "pregnant women", because DEEM does not evaluate lactating women.

J. Risk Characterization

1. Calculation of MOE

OEHHA agrees with the application of the PODs for exposure durations, except for one scenario, in the calculation of the MOEs. For the chronic exposure of handlers, the subchronic POD was used in calculating the MOE (Table 47; DPR, 2016a). The rationale was apparently because the season was only two months. For this scenario, OEHHA suggests using the chronic POD because the exposure from the 2-month season was amortized to 12 months to calculate the average exposure in the year (Table 6 of Appendix D; DPR, 2016a).

2. Target for Acceptable Risk

DPR considered the target MOE of 100 (which is the total UF) 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. As discussed in the section under Uncertainty Factors (Section III.G), OEHHA recommends target MOEs of 300 for all individuals, including sensitive populations such as infants and small children.

V. MINOR COMMENTS

Check the List of Abbreviations for missing abbreviations, and check consistency on format (e.g., LD_{50}, ppm instead of PPM), and typo (LOE(A)L and NOE(A)L).

Check document format (e.g., chemical name in lower case, citation of reports with multiple authors, add trend test to tables, duplicate text).

Draft RCD
- The draft RCD used both critical POD and critical NOEL interchangeably, to indicate the dose used to compare with human exposure levels for the calculation of MOE. OEHHA suggests using only the term "POD."
- The terminology used in the draft RCD regarding BMD modeling should be consistent with those provided in the output files, and the technical guidance (i.e. LED should be changed to BMDL and ED should be changed to BMD).
- It would be helpful to indicate in the Acute Toxicity and Subchronic Toxicity tables that the acute and subchronic PODs were derived from subchronic and chronic studies, respectively.
- In many places, incorrect terms (e.g., general population, ambient) were used to describe the residential bystander exposure to spray drift after application. On the other hand, exposure of the general population to propanil in the ambient air from area-wide use was not assessed. Some examples: **Page 1,** "ambient spray-drift," **Page 5, "**ambient spray-drift MOEs," **Page 12,** "ambient air," **Page 108,** "airborne propanil to the general population," and **Page 123,** "Drift Exposure Risk to the General Population."

Page 1, 3rd paragraph and Page 90, 2nd paragraph: RfD was defined as "the maximum, safe, daily exposure level."

This definition needs to be revised because it is not consistent with the US EPA definition:

> "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime…" from

> https://iaspub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossaries andkeywordlists/search.do?details=&vocabName=IRIS%20Glossary

Page 21: The third paragraph needs an explanation of "flip-flop kinetics".

Page 37: The shading in **Table 8** may not correct. MetHb formation of male and female mice of the Tompkins study (1993c) should be statistically significant at the low doses.

Page 44, Table 11: Why is only balanopreputial separation shown in the table? The text said there are other significant effects, such as sperm count, testes and liver weights. OEHHA suggests listing all relevant and significant effects in data summary tables.

Page 55, Table 16: Animal incidences for total pericholangitis (main group all) for both males and females were missing the % affected numbers.

Page 66-67, Table 21: No immunotoxicity effects were listed in the table yet the text states there were effects on splenic antibody production. OEHHA suggests including this data.

Page 95, under Subchronic Oral Toxicity: It states, "thirteen studies are included in the subchronic oral toxicity database" when it was actually 12 oral studies and one dermal study listed in Table 32.

Page 96: "3 subchronic feeding studies using dogs and with LED$_{1SD}$ values of (m/f) 0.7, 15, and a NOEL of < 5/6 mg/kg/day." There was no LED$_{1SD}$ of 0.7 mg/kg-day in the dog studies in the database. We assume this is a typo.

Page 108: The exposure equation appears to have the "n= ..." parenthetical multiplied by the parenthetical before it. Remove "n=…" from the equation.

Page 109, 1st paragraph:

- "Average estimates ... " in this paragraph applies to acute and chronic exposures but Table 39 shows only 95th-99th percentile values for acute exposures. Please revise appropriately.
- "geographic region" – not used in the draft RCD
- under "Anticipated Rice Residues"
  - "84 rough rice grain samples" – we count 26 samples (including duplicates). See comment for Table 35, below.
  - "during the 1992 ..." – should be "during 1990…"

Page 110, top of page: "... provided for comparison (Kinard, 2002)." The referenced info is not in Table 35.

Page 110, Table 35:

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- The sample sizes listed in parentheses in the 3rd column add up to 19, which when added to the 7 NDs of Ehn 2004 give a total of 26. This conflicts with the sample size of 84 given on p. 109 (see comment above)
- We agree with the values in the 3rd, 4th, and 5th columns but not with the values in the 6th and 7th columns (0.43 and 0.42) which differ from the values we calculated (0.506 and 0.499), respectively.

Page 111: "Maximum surrogate anticipated residue levels were identified for Propanil and 3,4-DCA and summed for acute exposure assessment." In contrast, the top of p. 116 states that average detected residues were used (this is under "Acute Dietary Exposure").

Page 111, Table 37:

- 1st row, 8th column: "(1 X LOD)" is confusing since the maximum detected value was used, which was a single value and no need for averaging with LOD values.
- 1st row, in the 8th and 9th columns: "(n)" is confusing, suggest deleting.
- 3rd row, 3rd column: the number in parentheses (sample number) is listed as 1972, which includes 16 data samples for which there is no LOQ and no detection level. Need to clarify how samples without an LOQ are determined to be nondetects. If this were not possible, then it would seem appropriate to remove these samples from analyses since they do not provide quantitative information. The sample size would then be 1972 – 16 = 1956.
- The referenced source for the ground water data are the annual summaries. It would be helpful to state that neither 3,4-DCA or propanil were analyzed 2001 – 2011, except propanil in 2002, 2003 and 2004. In the reports, the detected values were given as ranges rather than individual detected values. Reporting limits or detection limits were generally not provided. These two features of the reports result in inadequate data to derive an average water residue. In some of the reports, 3,4-DCA is reported as a possible degradate of linuron, diuron, and propanil; the uncertainty in there potentially being multiple sources of the degradate should be noted.

Page 111-112, Table 38:
- The table might be easier to understand if it were split in two tables with rice and water in one and animal products in the other. This would also help to clarify the title and eliminate the need for the "source" column.
- Footnote f): Specify what "default = 1" means.

Page 115, 1ˢᵗ paragraph: "... would be 500 or 1000 at the 95ᵗʰ or 99ᵗʰ percentile exposures respectively..." should be "1000 and 500 at the 95ᵗʰ and 99ᵗʰ percentile exposures, respectively."

Page 116:

- Top of page "Average detected levels of propanil and 3,4-DCA ..." This conflicts with page 111 (see comment, above) and is not applicable to acute exposure assessment.
- Top of page: "... were used as a surrogate for direct and indirect drinking water exposure." Is this for all sources of water?
- Paragraph after Table 40: "…The CEC identified rice…as making substantial (>10%) contributions to the overall acute dietary exposure…The…food forms…include white rice...(and) rice flour in baby food)…Additional information is needed for this point. Our analyses found rice flour baby food to contribute <10% to acute dietary exposure. It may be informative to include this so the reader understands that the >10% contribution noted is mainly from rice itself, if it is the case.

Appendix D: Occupational Exposure Assessment (refers to Draft HEAD)

The appropriate header for this Appendix is "Human Exposure Assessment for Propanil". Note that this assessment includes both workers (handlers and rice field workers) and residential bystander exposures, not only occupational exposures.

Page 11, paragraph 2: The HEAD lists three potential sources of uncertainty that may occur when a dermal/oral LOAEL ratio is used to estimate the dermal absorption rate, but provides no supporting citation. OEHHA suggests that the final HEAD include a reference.

Page 11, paragraph 2: A default dermal absorption valued of 50% was based on an internal analysis of 40 pesticides by DPR. However, the supporting documentation appears to be incomplete as OEHHA could identify only 26 of these pesticides in the cited reference (DPR, 1993). OEHHA suggests that identification of all 40 pesticides would increase the transparency of this default policy. Also, OEHHA suggests that the relevance of these 40 pesticides (e.g., structural similarity, molecular weight, chemical and physical properties) to propanil be discussed.

Page 12, paragraph 3: To emphasize that propanil spray drift exposure is primarily due to droplets and not vapor, OEHHA suggests that "...drift of *aerosolized* propanil during peak use periods is expected to be a *major* pathway of exposure…" to clarify the intent of this section.

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