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DATE: February 28, 2019

SUBJECT: Response to OEHHA Comments on the DPR Draft Propanil Risk Characterization Document (dated December 30, 2016) and charge questions (dated January 26, 2017)

I. Background

The Office of Environmental Health Hazard Assessment (OEHHA) in the California Environmental Protection Agency (Cal EPA) reviewed the draft Risk Characterization Document (RCD) for Propanil (December 30, 2016) and the corresponding memorandum with charge questions (January, 26 2017) prepared by the Human Health Assessment (HHA) Branch of the Department of Pesticide Regulation (DPR). OEHHA submitted their comments to HHA on March 23, 2017. This memorandum contains the Risk Assessment Section (RAS) responses to specific comments by OEHHA pertaining to the toxicology, hazard identification, dietary exposure and risk characterization sections of the RCD. Responses to comments pertaining to the Bystander and Occupational Exposure Assessment are covered in a separate memorandum.

The OEHHA review is divided into five parts: I. Summary of Review; II. Major Comments; III. Response to Charge Statements; IV. Detailed Comments; and V. Minor Comments. Because all of the issues raised by OEHHA in the first two sections are also covered in sections III and IV, HHA responses to those issues are largely relegated to the latter sections. Notes: references cited in the OEHHA review were not included in the reference section of this document; table references within HHA responses correspond to tables in this memorandum and not those in the draft or final RCD.

II. Responses to Charge Statements

A. Hazard Identification and Risk Characterization

Charge Question 1: A lowest effective dose (LED_{1SD}) 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 Comment: 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 1 SD for that effect as it is unclear what percentage of increased blood metHb levels in the animal studies would be considered adverse.

> **DPR HHA Response:** The critical, oral acute $BMDL_{1SD}$ was changed from 14.2 to 14.1 mg/kg/day in the final RCD. The revised point of departure (POD) was calculated using the data set for the same end-point but with correct group sizes (n) that were not available to HHA when the original POD was calculated using the corresponding US EPA study review as the data source. Corresponding sections of the RCD were revised to reflect this global change.

Charge Question 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 Comment: 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.

> **DPR HHA Response:** HHA reviewed the available open literature relevant to propanil-induced metHb formation. Based on the results of the review, we concluded that several subpopulations may have enhanced sensitivity to this effect, including young children, pregnant women, and people with hereditary deficiencies of the enzymes glucose-6-phosphate dehydrogenase or cytochrome b5 reductase. Therefore, an additional uncertainty factor (UF) of 3 was imposed to account for potentially enhanced sensitivity to metHb

formation in these populations. The RCD was revised to reflect this change. Additional information can be found in the Detailed Comments section of this memo.

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

OEHHA Comment: 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 7 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.

DPR HHA Response: HHA agrees that *in vivo* evidence suggests that 3,4-DCA has clastogenic activity in the male mouse (Eissa *et al.*, 2012). However, based on a reanalysis of tumor data from the rat and mouse in the propanil database, none of the tumors that were considered to have arisen from a putative genotoxic mode of action (MOA) (including hepatocellular adenomas in rats and mice and lymphoma in mice) had sufficient data for low-dose, linear extrapolation. Moreover, HHA maintains the original conclusion that (a) testicular interstitial tumors in the male rat were likely mediated by an endocrine MOA and that (b) the critical chronic oral POD based on hematologic toxicity would be protective. This was based on the comparison of the critical chronic POD for (1.5 mg/kg/day) with the chronic PODs for putative endocrine effects that included the most likely precursor (testicular focal interstitial hyperplasia) for the development of testicular interstitial tumors ($\geq$ 11.2 mg/kg/day). A discussion of this reanalysis and the conclusions that were reached are in the *Detailed Comments* section of this memo.

III. Detailed Comments

A. Pharmacokinetics

OEHHA Comment: 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 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.

> **DPR HHA Response:** The draft RCD text was revised to correct the error identified on pg. 20 of the draft RCD.

OEHHA Comment (continued): 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.

DPR HHA Response: To clarify, the term “primary amine” was used in the *Chemical Identification* section to describe a chemical functional group. On the other hand, the terms “primary”, “secondary”, and “tertiary” were used to categorize metabolites based on their metabolism and presumed relative hematologic toxicity. HHA still considers the rationale, as described in the *Toxicological Profile-Metabolism and Pharmacokinetics* section, to be adequate and clear for its intended purpose in the RCD.

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

OEHHA Comment: 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.

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 LD50 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 (See original OEHHA Document Review), 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.

DPR HHA Response: The only scenarios likely to involve direct, toxicologically-relevant exposures to 3,4-DCA are those corresponding to dietary intake. Occupational and bystander exposures by dermal, inhalation, and cumulative deposition routes are likely to be entirely in the form of propanil parent. The PODs used for estimating the risks of acute and chronic dietary exposures to propanil were based on registrant submitted studies using propanil as the test article. The data for 3,4-DCA were limited which often precluded the direct comparison of threshold toxicities for the parent and metabolite. Nevertheless, what comparisons could be made suggested that the use of critical acute and chronic PODs based on the toxicity of propanil parent would be protective for acute and chronic dietary exposures to propanil residues convertible to 3,4-DCA without the application of an additional UF. A more detailed discussion was added to the *Risk Appraisal-Issues Related to Metabolites, Contaminants, and Co-Formulated AIs-3,4-DCA* section of the final RCD.

OEHHA Comment (continued):

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 1 SD for continuous data and 10% for quantal data.

OEHHA agrees with the use of a BMR of 1 SD 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 1 SD 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).

DPR HHA Response: No response necessary.

OEHHA Comment (cont.): 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.

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

DPR HHA Response: HHA considers the effect incidence levels, severity, and group size when selecting BMR levels. The HHA default BMR for quantal data is 10% based on the level recommended in the US EPA Benchmark Dose Technical Guidance document for comparing BMDL values (the lower 95% confidence interval of the BMD) across endpoints (USEPA, 2012).

HHA considers the 10% BMR level appropriate for the chronic BMDL (0.5 mg/kg/day) based on splenic hemosiderosis data reported in the 2-year rat chronic feeding and carcinogenicity study with propanil. This was based on the sizes of the treatment groups for the total incidence of hemosiderosis in male rats at terminal sacrifice (104 weeks) (n = 15 to 21) and for the level of severity observed for the end-point.

We further analyzed the data based on OEHHA comments and concluded that the chronic POD should be based on the total incidence of all-severity hemosiderosis in all of the main group male rats (see HHA response to OEHHA comments regarding Chronic Oral Toxicity Evaluation). Hemosiderosis was one part of a pattern of splenic toxicity that also included organ enlargement and increased organ weight. This pattern of organ toxicity, with a dataset that now included 50 animals per group, was still considered to support the use of a 10% BMR and resulted in a $BMDL_{10}$ of 1.5 mg/kg/day. The final RCD now reflects the changes described above.

C. Acute Oral Toxicity Evaluation

OEHHA Comment: 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 $BMDL1_{SD}$ (referred to as the $LED1_{SD}$ 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 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 nondietary studies, indicating these effects could not be attributed to diet palatability issues.

DPR HHA Response: Based on the corresponding OEHHA comment, the original justification for the selection of the acute, oral BMDL given in the *Risk Appraisal-Hazard Identification-Acute Oral Toxicity* section of the RCD was revised to strengthen its underlying rationale.

D. Subchronic Oral Toxicity Evaluation

OEHHA Comment: 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- 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.

DPR HHA Response: No response necessary.

E. Chronic Oral Toxicity Evaluation

OEHHA Comment: 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 1 SD, 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.

DPR HHA Response: The RCD was revised to reflect changes to critical PODs made in response to the above comments.

OEHHA Comment: 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 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.

DPR HHA Response: The splenic hemosiderosis data were reanalyzed based on OEHHA's comments. The first incidental splenic hemosiderosis finding was at week 29, prior to the first mortality in any group. Clear and consistent dose responses were observed for minimal and moderate severities in males while no dose responses were observed for any severity in females (Table 1). The analysis that led to the original POD also included a consideration of the potential relationship of severity to treatment level; no new conclusions were reached with reanalysis. The lack of dose responsiveness observed for the female rats may rest more on the high rate of incidence for splenic hemosiderosis in the female control group than physiological gender differences related to key steps in the hematologic toxicity of propanil. Whatever the bases for the observed differences, they cannot be explained away by the data. HHA still considers the splenic hemosiderosis incidence data in male rats to be an effect of treatment because it is supported by a well-defined MOA for propanil, patterns of splenic and kidney toxicity in male and female rats in the same study, and patterns of chronic splenic toxicity in other studies with mice and dogs.

On the other hand, HHA concluded that the original approach using incidence data from animals surviving to week 104 might introduce uncertainty into the derivation of chronic POD. For this reason, the re-analysis focused on the data from all main group animals rather than on survivors and considered all severities with clear and consistent dose responses. The lowest POD based on splenic hemosiderosis in male rats was for all severities (BMD_{10}/$BMDL_{10}$ = 2.3/1.5 mg/kg/day) (Table 1). PODs based on multiple liver endpoints including pericholangitis were considered in the original analysis but none was selected because they were all higher than the POD for splenic hemosiderosis. This was still the case when PODs were calculated using total incidence data (Table 2). The RCD was revised to reflect the changes described above.

Table 1. Propanil-Induced Splenic Hemosiderosis in a 2-Year Chronic Carcinogenicity Study with CD Rats (Bellringer, 1994)

Sex	Male	Male	Male	Male	Female	Female	Female	Female
Dose (ppm):	0	200	600	1800	0	200	600	1800
Main Group Dose (mg/kg/day):	0	9	28	88	0	12	38	145
N (main):	50	50	50	50	50	50	50	50
Splenic Hemosiderosis: Incidences/Total Animals (Main Group All)								
Trace	4	7	6	4	6	1	3	10
Minimal	4	11	16	18	27	16	16	22
Moderate	2	5	12	15	12	14	13	14
Marked	1	0	0	5	3	0	2	0
Total (all severities)	11	23	34	42	48	31	34	46

Table 2. Summary of Chronic BMD Results for Propanil Effects with Liver and Spleen End-Points

Exposure Duration and Route	Study Type/Ref.	End-Point	Sex	Timing	Data Type	BMR	Model(s)	BMD (mg/kg/day)	BMDL(mg/kg/day)
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Spleen Hemosiderosis (total)	m	All Main	Quantal	10%	Log-Logistic	2.3	1.5
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Spleen Hemosiderosis (minimal)	m	All Main	Quantal	10%	Log-Logistic	19.2	10.6
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Spleen Hemosiderosis (moderate)	m	All Main	Quantal	10%	Log-Logistic	20.9	12.9
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Spleen Hemosiderosis (minimal and moderate)	m	All Main	Quantal	10%	Log-Logistic	4.4	2.9
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Liver: Pericholangitis (total)	m	All Main	Quantal	10%	Log-Logistic	7.3	3.1

F. Inhalation Toxicity Evaluation

OEHHA Comment: 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.

DPR HHA Response: HHA considers the selection of the acute and subchronic oral PODs ($BMDL_{1SD}$ = 14.1 and 5.0 mg/kg-day, respectively) based on increased metHb levels rats after 5 days and 13 weeks of treatment to be the most supportable based on considerations of exposure duration, route, metabolism, and bioavailability. This selection was based on the following:

The only significant scenarios leading to direct exposures to 3,4-DCA resulting from environmental propanil metabolism or degradation are those for dietary consumption on food or drinking water. Occupational or bystander exposure scenarios have an inhalation exposure component, but in both cases the only significant exposure will be to propanil parent and not to 3,4-DCA or any other species. Moreover, there are presently no mammalian absorption, distribution, metabolism, and excretion (ADME) data for the inhalation exposure to propanil. Neither is there evidence for aryl-acylamidase activity in the rodent or human lung. The latter suggests the possibility that, by either exposure route, the liver will be the site where the key steps to toxic activation occur.

Therefore, using a surrogate POD for propanil based on the inhalation toxicity of 3,4-DCA would introduce unique uncertainties because inhalation exposure for humans is not expected to occur directly from 3,4-DCA. Additional uncertainties would result from the use of subchronic PODs based on effects of 3,4-DCA or propanil to estimate the risk of acute exposures. While there are uncertainties intrinsic to the assumptions of (a) inhalation bioavailability (100%) and (b) metabolic equivalency for oral and inhalation routes, HHA is of the opinion that they are not likely to lead to an underestimation of internal exposure or risk. The conservative nature of this approach lies largely with the bioavailability assumption.

G. Dermal Toxicity Evaluation

OEHHA Comment: The toxicity database for propanil dermal exposure included dermal LD50 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.

DPR HHA Response: No response necessary.

H. Reproductive and Developmental Toxicity

OEHHA Comment: 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.

DPR HHA Response: No response necessary.

I. lmmunotoxicity

OEHHA Comment: 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 lgM 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 lgG1, 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.

DPR HHA Response: We identified all published studies reporting the immunotoxicity of propanil in the results of literature searches conducted between 2012 and 2016. This was done in order to identify data that could be used to develop or support a critical POD and/or MOA. Studies were screened for relevance, and a subset was given a more comprehensive review (Table 3). The animal studies all used an intraperitoneal (IP) route and, as such, their data were not considered suitable for the development of a POD that could be used to assess the risk of propanil. The IP route is most similar to the intravenous route (IV) because both bypass absorption barriers and initial metabolism in the liver and/or lungs that are key aspects of the exposures of concern in the risk assessment of propanil. On the other hand, there is concern for the immunotoxicity of propanil and the animal studies are useful because they provide insight into putative MOAs and critical endpoints for the evaluation of toxicity. For this reason, select studies were summarized in the *Chemical Identification* and *Toxicity Profile-Immunotoxicity* sections. On the basis of the reviewer's comments, additional text was added to the *Risk Appraisal-Hazard Identification-Immunotoxicity* section of the final RCD to describe its consideration and use in the development of critical POD values.

Table 3. Summary of Open Literature Immunotoxicity Studies for Propanil (Technical and Formulations)

Study Type	Species	Dose Levels and Route (male/female mg/kg)	NOEL (mg/kg)	LOEL (mg/kg) and Critical Endpoints	References
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 100, 150, and 200 (i.p. route)	Acute < 100	Acute = 100 ↓thymic cellularity (CD3 +/-)	(Zhao *et al.*, 1995)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 50, 100, 150, and 200 (i.p. route)	Acute < 50	Acute = 50 ↑ induction of corticosterone Note: the immunotoxicities of propanil and 2,4-D were tested alone and as a mixture.	(de la Rosa *et al.*, 2005)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 100, and 200 (i.p. route)	Acute = 100 Or < 200 thymus-to-body weight only	Acute = 200 ↓thymic cellularity and relative thymus weight, and ↓ double positive ($CD4^+CD8^+$) cell counts.	(Cuff *et al.*, 1996)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0 and 200 (i.p. route)	Acute < 200	Acute = 200 ↓levels of liver and spleen IFN-γ (in vivo exposure and ex vivo induction and assay) liver IL-6 and spleen TNF-α (in vivo exposure) ↑levels of liver IL-1β (in vivo exposure) and serum IL-6 following intentional bacterial infection.	(Watson *et al.*, 2000)

Table 3. Summary of Open Literature Immunotoxicity Studies for Propanil (Technical and Formulations)

Study Type	Species	Dose Levels and Route (male/female mg/kg)	NOEL (mg/kg)	LOEL (mg/kg) and Critical Endpoints	References
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 10, 25, 50, 100, 200, and 400 (i.p. route)	Acute = 100	Acute = 200 ↑spleen-to-body weights and cellularity, and thymus-to-body weights.	(Barnett and Gandy, 1989)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0 and 200 (i.p. route) 0, 40, and 400 (oral gavage)	i.p. Acute < 200 Oral Acute < 40	i.p. Acute = 200 ↓levels of macrophage IL-6 and TNFα (in vivo exposure and ex vivo induction and assay). Oral Acute = 40 ↓levels of macrophage IL-6 and TNFα (in vivo exposure and ex vivo induction and assay).	(Xie *et al.*, 1997 (a))
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	Propanil: 0, 50, 100, and 200 3,4-DCA: 0, 37, 75, 150 (i.p. route)	Propanil: Acute < 50 3,4-DCA: Acute < 37	Propanil: Acute = 50 ↓NK cell activity (in vivo exposure and ex vivo assay) 3,4-DCA: Acute = 37 ↑levels of splenic antibody production (in vivo exposure and immunization and ex vivo induction and assay). Notably but not significantly ↓NK cell activity (in vivo exposure and ex vivo assay) was also reproducibly observed at the above dose level for 3,4-DCA .	(Barnett *et al.*, 1992)
Acute and Subchronic *In Vivo* Immunotoxicity Open Literature	Mouse	0, 50, 75, 100, and 150 (i.p. route)	Acute < 50	Acute = 50 ↓lymphocyte counts, increased neutrophil counts, ↓MHC Class II expression by B lymphocytes in blood and spleen, proportion of B lymphocytes in blood, ↓$CD4^+$ and $CD8^+$T-cell counts in blood, and ↓NK cell activity (in vivo exposure and ex vivo assay) Subchronic (28 day) = 50 mg/kg/day Based on ↓ lymphocyte counts, ↑ neutrophil counts, ↓ MHC Class II expression by B lymphocytes in spleen, ↓ proportion of B lymphocytes in spleen, and ↓ NK cell activity (in vivo exposure and ex vivo assay).	(Pruett *et al.*, 2009)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 50, 100, 150, and 200 (i.p. route)	Acute < 50	Acute = 50 Based on ↓ numbers of bone marrow pre-B cells. Note: the immunotoxicities of propanil and 2,4-D were tested alone and as a mixture.	(de la Rosa *et al.*, 2003)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 50, 100, and 200 (i.p. route)	Acute < 50	Acute = 50 Based on ↓ viable myeloid stem and progenitor cells (CFU-IL-3 and CFU-GM) counts in bone marrow.	(Blyler *et al.*, 1994)

Table 3. Summary of Open Literature Immunotoxicity Studies for Propanil (Technical and Formulations)

Study Type	Species	Dose Levels and Route (male/female mg/kg)	NOEL (mg/kg)	LOEL (mg/kg) and Critical Endpoints	References
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0 and 150 (i.p. route)	Acute < 150	Acute = 150 Based on ↑ counts of splenic antibody secreting cells (ASCs).	(Salazar *et al.*, 2006)
Acute *In Vivo* Immunotoxicity Open Literature	Mouse	0, 25, 50, 100, and 150 (i.p. route)	Acute = 25	Acute = 50 Based on ↑ counts of splenic antibody secreting cells (ASCs) Note: the immunotoxicities of propanil and 2,4-D were tested alone and as a mixture.	(Salazar *et al.*, 2005)
Subchronic (30 Day) Population-Based Immunotoxicity Open Literature	Human	All route exposure estimates based on measured urinary levels of 3,4-DCA in day +30 sample: Control Cohort: 0 ng/mL (*BLQ*) Exposed Cohort: 105.6 (7.4-331.9) ng/mL	NA	Propanil exposure-related and statistically significant changes included: ↑ serum levels of IgG_1 ↑ levels of IL-6 and ↓ levels of IL-10 and IFN (ex vivo induction and assay)	(Corsini *et al.*, 2007)

J. Carcinogenicity Weight of Evidence

OEHHA Comment: 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.

DPR HHA Response: Detailed responses are provided in the *Genotoxicity and Experimental Animal Evidence* subsections of this memo.

i. Genotoxicity

OEHHA Comment: 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 etal. (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 (see OEHHA Document Review).

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; See original OEHHA Comments document).

DPR HHA Response: HHA reviewed the genotoxicity and clastogenicity studies (Osano *et al.,* 2002; Eissa *et al.,* 2012) cited by OEHHA and added reviews of both to the Toxicity Profile of 3,4-DCA in the final RCD. The clastogenicity study (Eissa *et al.,* 2012) provides compelling evidence that propanil may have genotoxic activity mediated by its metabolite, 3,4-DCA. The final RCD now reflects the changes described above.

ii. Experimental Animal Evidence

OEHHA Comment: 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; See original OEHHA Comments document). 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 1 05; 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 1 06; DPR, 2016a).

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; see OEHHA Document Review). 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 $(mg/kg\text{-}day)^{-1}$ (Table 3; see OEHHA Document Review).

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.

> **DPR HHA Response:** As stated above, newly-introduced *in vivo* evidence suggests that 3,4-DCA and, based on metabolic fate, propanil have potential genotoxic activities. However, based on a reanalysis of tumor data from the rat and mouse in the propanil database, none of the tumors that were considered to have arisen from a putative genotoxic MOA had data that was sufficient for low-dose, linear extrapolation. Each of the aforementioned tumors will be discussed below.
>
> The increased incidence of benign hepatocellular adenomas in female rats in the high dose group appeared to be the result of propanil treatment (Table 4). This effect was not considered suitable for low-dose, linear extrapolation because it lacked a clear and consistent

dose response and statistical significance (Fisher's Exact Test) in any dose group. Additionally, there were no hepatocellular carcinomas in the same female dose groups and no clear treatment-related increases in hepatocellular adenomas or carcinomas in male rats.

Hepatocellular adenomas in male mice were also not considered suitable for low-dose, linear extrapolation because incidence data failed to reach statistical significance for pairwise comparisons at any dose level or for dose responsive trends in Cochran-Armitage, and Poly 3 Tests (Table 5). In addition, there were no consistent, treatment-related increases in hepatocellular carcinomas in male or female mice.

The increased incidence of malignant lymphomas (all tissues) in female mice at the high dose also appeared to be the result of propanil treatment (Table 5). This effect was not considered suitable for low-dose, linear extrapolation because it was only apparent at the high dose.

Benign testicular interstitial tumors in the male rat were not considered for linear, low-dose extrapolation because these tumors likely resulted from propanil-mediated disruption of androgen signaling leading to increased pituitary LH secretion (Table 4). We considered this to be a threshold effect with neoplastic consequences in target tissues. Several observations support an LH-dependent mode of action: (a) propanil weakly binds to the rat androgen receptor *in vitro* (McCarroll, 2012); (b) there was an increased incidence of testicular focal interstitial hyperplasia combined with absent epididymal spermatozoa, reduced secretions in seminal vesicles, and prostate atrophy in male rats in the same study; and (c) delayed balanopreputial separation was observed in male rat pups in a two-generation reproductive toxicity study (Stump, 1998). All of these effects were likely mediated by propanil through disruption of the pituitary-testicular axis, with testicular tumors as a long term consequence.

Measurements of serum androgen and luteinizing hormone (LH) levels in response to propanil did not show changes that could be linked directly to the effects described above (Stump, 1998). However, the intrinsic pulsatile nature of androgen and LH levels can create a level of variability in these parameters that makes it difficult to detect subtle, treatment-related changes (Bartke *et al.*, 1973; Dong and Handelsman, 1989).

Further support for a threshold MOA comes from study data for linuron, an anilide herbicide with a similar molecular structure and modes of herbicidal and mammalian toxicity to propanil (USEPA, 2016). For example, linuron has receptor mediated anti-androgenic activity, induces tissue-level effects in the sex and accessory sex organs of male rats, and increases the incidence of benign testicular interstitial tumors (USEPA, 2015). One study by

Makris (1991), in particular, clearly demonstrated an MOA for testicular interstitial cell tumors mediated by the anti-androgenic activity. Key events in the putative MOA included competitive antagonism by binding to the androgen receptor (AR) leading to hypersecretion of LH.

The PODs ($BMDL_{10}$) for the putative endocrine effects described above range from 11.2 to 37.5 mg/kg/day, while the POD for the most likely tumor precursor (testicular focal interstitial hyperplasia) is 19.6 mg/kg/day (Table 6). The lowest POD discussed above is 7.5 fold higher than the critical chronic oral POD based on splenic hemosiderosis ($BMDL_{10}$ = 1.5 mg/kg/day). Taken together, these data suggest that the critical chronic oral POD will be protective of effects mediated by the putative endocrine MOA. The *Hazard Identification and Risk Appraisal-Oncogenicity Weight of Evidence* sections of the final RCD now reflect the revised rationale described above. Additionally, a human slope or potency factor was calculated so that the chronic lifetime cancer risk could be estimated and discussed in the *Risk Appraisal-Oncogenicity Weight of Evidence* section.

Table 4. Propanil-Induced Tumor Effects in a 2-Year Chronic Carcinogenicity Study with CD Rats (Bellringer, 1994)

Sex	Male	Male	Male	Male	Female	Female	Female	Female
Dose (ppm):	0	200	600	1800	0	200	600	1800
Main Group Dose (mg/kg/day):	0	9	28	88	0	12	38	145
N (main):	50	50	50	50	50	50	50	50
Legend:	p < 0.05				p < 0.01			
Neoplastic Findings (No. Animals with Tumors/No. Animals per Group At Risk)								
Testes: Benign Interstitial Cell Tumor (Total/At Risk on Week 86[3]) [2]	3/39	3/34	8/40	29/40***	NA	NA	NA	NA
Liver: Benign Hepatocellular Adenoma (Total/At Risk on Week 84/79 (m/f)[3]) [2]	0/39	3/34	0/40	0/40	1/37	0/40	1/41	6/47
Liver: Hepatocellular Carcinoma (Total/At Risk on Week 84/79 (m/f)[3]) [2]	1/39	0/34	3/40	0/40	0/37	0/40	0/41	0/47

[2] Statistical analysis performed by DPR: Fisher's Exact Test (*** p < 0.001)
[3] The number of animals at-risk for each tumor type and gender was based on the number of animals in each dose group that were alive during the 5-week window immediately preceding the death of the animal with the first identified tumor in any dose group.

Table 5. Propanil-Induced Tumor Effects in a 2-Year Chronic Carcinogenicity Study with CD-1 Mice (Tompkins, 1994)

Sex	Male	Male	Male	Female	Female	Female
Dose (ppm):	**0**	**500**	**1000**	**0**	**500**	**1000**
Dose (mg/kg/day):	**0**	**75**	**150**	**0**	**89**	**174**
n:	**80**	**80**	**80**	**80**	**80**	**80**
Legend:	**p < 0.05**			**p < 0.01**		
Neoplastic Findings: (No. Animals with Tumors/No. Animals per Group Examined or At Risk)						
Malignant Lymphoma All Tissues (Total/At Risk on Week 21/32 (m/f)[2])[1] (f only)	3/61	4/63	1/60	4/59	4/59	13/58
Hepatocellular Adenoma /At Risk on Week 52/102 (m/f) [1,2] (m only)	8/58	9/57	11/56	1/26	2/27	1/24
Hepatocellular Carcinoma /At Risk on Week 52/102 (m/f) [2] (m only)	3/58	1/57	0/56	0/26	0/27	0/24

[1]Statistical analysis performed by DPR: Fisher's Exact Test.
[2]The number of animals at-risk for each tumor type and gender was based on the number of animals in each dose group that were alive in the week immediately preceding the death of the animal with the first identified tumor in any dose group.

Table 6. Summary of Chronic BMD Results for Propanil Effects with Potential Endocrine Disruption End-Points

Exposure Duration and Route	Study Type/Ref.	End-Point	Sex	Timing	Data Type	BMR	Model(s)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Rel. Testes Wt.	m	Week 52	Continuous	1SD	Linear, Polynomial 2 and 3, and Power	47.4	37.5
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Testicular Focal Interstitial Hyperplasia (total)	m	All Main	Continuous	1SD	Multistage 2	25.6	19.6
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Absent Spermatozoa in Epididymides	m	All Main	Quantal	10%	Log-Logistic	35.8	15.1
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Reduced Secretions in Seminal Vesicles	m	All Main	Quantal	10%	Log-Logistic	23.1	11.2
Chronic; Oral	Chronic and Carcinogenicity; 2-year; Rat (Bellringer, 1994)	Prostate Atrophy (total)	m	All Main	Quantal	10%	Multistage 2	58.2	32.2

Table 6. Summary of Chronic BMD Results for Propanil Effects with Potential Endocrine Disruption End-Points

Exposure Duration and Route	Study Type/Ref.	End-Point	Sex	Timing	Data Type	BMR	Model(s)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Subchronic; Oral	2-Generation Reproductive Toxicity; Rat (Stump, 1998)	Timing for completion of balanopreputial separation.	m and f	NA	Continuous	1SD	Linear, Polynomial 2 and 3, and Power (Model Variance) *Note: SDobs/SDest = 83%*	24.6	18.2

K. Uncertainty Factors

i. lnterspecies Extrapolation

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

DPR HHA Response: No response necessary.

ii. lntraspecies Extrapolation

OEHHA Comment: 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).

DPR HHA Response: HHA addressed the potential enhanced sensitivity of children and adult subpopulations to chemical mediated metHb formation by imposing an addition 3-fold factor raising the UF_{total} from 100 to 300. The RCD was revised to reflect this change.

i. Physical and Chemical Properties, and Environmental Fate

OEHHA Comment: 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).

DPR HHA Response: A *Volatility* sub-section and text was added to the *Environmental Fate-Physicochemical Properties* section of the final RCD.

OEHHA Comment: 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.

DPR HHA Response: No response necessary.

ii. Pesticide Use and Application

OEHHA Comment: 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.

DPR HHA Response: The *Risk Appraisal-Anticipated Drinking Water Residue Data* section of the final RCD was added based on the OEHHA comments.

OEHHA Comment: 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.

DPR HHA Response: The final RCD now contains updated pesticide usage data through 2015. See the response to exposure assessment comments for additional information.

iii. Reported Illness

OEHHA Comment: 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.

DPR HHA Response: The report cited by OEHHA was reviewed and relevant information was incorporated in the *Illness Reports* section of the final RCD. See the response to exposure assessment comments for additional information.

OEHHA Comment: 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.

DPR HHA Response: No response necessary.

iv. Dietary Exposure Assessment

OEHHA Comment: 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.

DPR HHA Response: No response necessary.

Residue Data

OEHHA Comment: 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 A I)/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.

DPR HHA Response: Per OEHHA's comments, the PCT factor was recalculated using the correct formula. The corrected PCT (75%) was then used to calculate chronic dietary risk. Corresponding sections of the final RCD (*Exposure Assessment -Estimate for Percentage of CA Rice Crop Treated,* etc.*)* now reflect this global change.

Exposure Calculation using DEEM-FCID

OEHHA Comment: 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.

DPR HHA Response: The DEEM chronic module uses the NHANES two-day average food consumption data to calculate the average, per capita chronic dietary exposure while the DEEM acute module can use the two-day consumption data to calculate per user and per capita exposures. We used the acute DEEM module to estimate the per user and per capita exposures from consumption of rice-based foods to assess the degree to which chronic, per capita exposures may underestimate the exposure risk for propanil. These analyses used input data from the chronic residue file and the propanil chronic POD (1.5 mg/kg/day). The per capita and per user exposures and corresponding MOEs were then compared (Table 7). The

per user and per capita exposures were essentially the same for all of the evaluated subpopulations, except for the Nursing Infants and All Infants subpopulations that had per user exposures that were 24% and 7 % higher than per capita. Regardless, the corresponding per user MOEs for both subpopulations were over 10 fold greater than the target MOE (300) and, as such, did not indicate a health concern.

Table 7. A Comparison of Per Capita and User Acute 2-Day Dietary Exposures and Corresponding MOEs

Subpopulation	Percentage of Individuals That are Users (%)	Per Capita 2-Day Average Exposure (mg/kg/day)	User 2-Day Average Exposure (mg/kg/day)	Per Capita 2-Day Average MOE	User 2-Day Average MOE
Total US Population:	99.89%	0.000157	0.000158	9532	9521
Hispanic:	99.84%	0.000214	0.000214	7008	6997
Non-Hisp-White:	99.90%	0.000131	0.000131	11419	11408
Non-Hisp-Black:	99.94%	0.000162	0.000162	9280	9275
Non-Hisp-Other:	99.84%	0.000349	0.000349	4301	4294
Nursing Infants:	76.20%	0.000230	0.000302	6521	4969
Non-Nursing Infants:	99.96%	0.000435	0.000436	3445	3443
All Infants:	92.62%	0.000372	0.000402	4032	3735
Female 13-50:	100.00%	0.000118	0.000118	12707	12707
Children 1-2:	100.00%	0.000386	0.000386	3881	3881
Children 3-5:	100.00%	0.000321	0.000321	4678	4678
Children 6-12:	100.00%	0.000200	0.000200	7499	7499
Adults 50-99:	100.00%	0.000108	0.000108	13948	13948

OEHHA Comment: 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.

DPR HHA Response: The only appearance of the term "pregnancy/lactation" in the draft RCD was in the *Dietary and Drinking Water Exposure-Introduction* section. The corresponding text was revised per OEHHA's comment.

L. Risk Characterization

i. Calculation of MOE

OEHHA Comment: 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).

DPR HHA Response: The critical chronic oral POD was used to calculate the risk of annual occupation exposure in the final RCD.

ii. Target for Acceptable Risk

OEHHA Comment: 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.

DPR HHA Response: HHA addressed the potential enhanced sensitivity of children and adult subpopulations to chemical mediated metHb formation by imposing an addition 3-fold UF raising the UF_{total} to 300. The final RCD now reflects this change.

IV. MINOR COMMENTS

OEHHA Comment: Check the List of Abbreviations for missing abbreviations, and check consistency on format (e.g., LD50, ppm instead of PPM), and typo (LOE(A)L and NOE(A)L).

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

DPR HHA Response: The RCD was reviewed and revised to correct any instances of the findings in the above two comments.

OEHHA Comment: 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."

DPR HHA Response: The RCD was revised to clarify that the term POD refers to experimentally determined (i.e., NOELs) and data derived no-effects levels (i.e. BMDLs and ENELs) considered in the hazard identification section including those considered critical to the risk assessment.

OEHHA Comment: 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).

DPR HHA Response: The final RCD now shows consistent use of the terms BMD and BMDL for BMD-derived PODs.

OEHHA Comment: 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.

DPR HHA Response: The tables discussed above correspond to tables in the *Hazard Identification* section of the draft RCD and summarize respective acute and subchronic POD values. The summary of acute POD values was revised to better identify acute studies in the final RCD.

OEHHA Comment: 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."

DPR HHA Response: In the final RCD the term “residential bystander exposure” was used consistently to describe any non-occupational exposures to spray-drift. The term “General Population” was retained to describe aggregate exposures with no occupational components.

OEHHA Comment: 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/gIossaries andkeywordlists/search.do?details=&vocabName=IRIS%20Glossary

DPR HHA Response: The RCD was revised to include the US EPA definition of a reference dose (RfD).

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

DPR HHA Response: The *Human Pharmacokinetics and ADME Studies-Pharmacokinetics* section of the final RCD now includes a brief explanation of "flip-flop kinetics".

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

DPR HHA Response: The corresponding male and female metHb data were reanalyzed using a 1-way ANOVA with Dunnett's post-test (GraphPad Prism 7.00). The male data was statistically significant at the low dose level ($p < 0.05$) and the original statistical significance was confirmed for the female data. The corresponding tables in the final RCD now reflect the new result in the males.

OEHHA Comment: 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.

DPR HHA Response: While all toxicologically significant effects were described in the summary review for each study included in the *Toxicity Profile* section, only data from select studies were included in tabular format. In general, data used to calculate a BMD/BMDL were included in a table for the sake of transparency. Data were also included in a table if

they provided support for a critical POD. The summary reviews in the final RCD are sufficient to document the toxicity of propanil. The most current Toxicology Data Review Summary for Propanil (May 2016) is also appended to the final RCD.

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

DPR HHA Response: The corresponding table was revised to correct this omission.

OEHHA Comment: 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.

DPR HHA Response: The splenic antibody production end-point data was described in the summary review for the corresponding study that was included in the *Toxicity Profile* section. It was not included in the table or used to develop a critical POD for risk assessment because it lacked statistical significance and a consistent dose response.

OEHHA Comment: 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.

DPR HHA Response: Following re-review, the corresponding RCD table was revised to include PODs from fourteen studies.

OEHHA Comment: 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.

DPR HHA Response: Per the above OEHHA comment, corresponding text was revised.

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

DPR HHA Response: Corresponding text was revised per the above OEHHA comment.

OEHHA Comment: 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 ... "

DPR HHA Response: Subsequent to re-review, text corresponding to the above comments was revised.

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

DPR HHA Response: Subsequent to re-review per the above OEHHA comments, corresponding text was revised.

OEHHA Comment: Page 110, Table 35:

- The sample sizes listed in parentheses in the 3'd 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.

DPR HHA Response: The rice residue data used for dietary risk assessment included 31 total sample measurements with 19 resulting in the detection of residues exceeding the corresponding LODs. With regards to this data, the corresponding table and text in *the Exposure Assessment-Dietary and Drinking Water Exposure-Anticipated Rice Residues* section were found to be correct and in harmony. The original average residue levels using either 1 or ½ LOD levels were found to be correct following re-review.

OEHHA Comment: 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").

DPR HHA Response: Subsequent to re-review per the above OEHHA comments, corresponding text was revised.

OEHHA Comment: 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.

DPR HHA Response: Subsequent to re-review per the above OEHHA comments, corresponding table text was revised to (a) only include samples with a reported analytical result or an LOQ and (b) more clearly report the sample dates for the ground water data used. The reference for the source of the ground water residue data was also revised to clarify that individual sample data were obtained from Well Inventory Database, Pesticide-Summary Tables(http://www.cdpr.ca.gov/docs/emon/grndwtr/well_inventory_database/pesticide_summary.htm) and not the Annual Summaries.

The *Risk Appraisal-Exposure Assessment-Dietary Exposure Assessment-3,4-DCA Residue Considerations* section was to revised to include a brief discussion of the uncertainties arising from the origin of 3,4-DCA residues.

OEHHA Comment: 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.

DPR HHA Response: The table in question was constructed to provide a direct correlation with the DEEM residue files used to estimate dietary exposure and risk, and as such provides optimal traceability. The footnote “f” text ("default = 1") was deleted for clarity.

OEHHA Comment: 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."

DPR HHA Response: The corresponding text in the *Exposure Assessment-Acute Dietary Exposure* section was revised per the above OEHHA comments and in consideration of the revised UF_{total} (300).

OEHHA Comment: 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.

DPR HHA Response: Corresponding text in the *Exposure Assessment-Dietary and Drinking Water Exposure-Acute Exposure Assessment- Tier 1 Point Estimate Assessment* section was revised for clarity per the first two OEHHA comments**.** New Acute Tier 2 and 3 exposure assessments were performed in the process of preparing the revised RCD. A new Critical Exposure Commodity (CEC) analysis was performed as part of the Tier 3 assessment. The corresponding text and table in the *Exposure Assessment-Dietary and Drinking Water*

Exposure- Acute Exposure Assessment - Tier 3 Mixed Point and Probabilistic Assessment section was drafted per the OEHHA comment regarding the previous CEC analysis.

HHA thanks OEHHA for their careful review of our work. The corrections will appear in the final RCD where appropriate.

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