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MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: May 31, 2013

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR PROPARGITE

The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed the draft Risk Characterization Document (RCD) for occupational and ambient air exposure to propargite, prepared by the Department of Pesticide Regulation (DPR), dated July 12, 2012. Our comments are provided in the attachment. OEHHA is currently reviewing the Exposure Assessment Document for Propargite and will be sending comments on that document separately. OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agriculture Code section 11454.1.

OEHHA has several general comments on the risk assessment methodology and conclusions of the draft RCD. These comments and our recommendations, as well as suggested clarifications, additions and correctio

Thank you for providing this draft document for our review. If you have any questions regarding OEHHA's comments, please contact Dr. Charles Salocks at (916) 323-2605 or Dr. Anna Fan at (510) 622-3200.

Attachment

cc: George V. Alexeeff, Ph.D., D.A.B.T.
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OEHHA's Comments on DPR's Draft (July 12, 2012)
Risk Characterization Document for Propargite
(Occupational and Ambient Air Exposures)

The Office of Environmental Health Hazard Assessment (OEHHA) is responding to a request from the Department of Pesticide Regulation (DPR) to comment on the draft Risk Characterization Document (RCD) for propargite. The document addresses occupational and ambient air exposures.

OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agricultural Code Section 11454.1, which requires OEHHA to conduct scientific peer reviews of risk assessments conducted by DPR.

SUMMARY

The RCD was comprehensive and well-written with thorough presentation of the toxicological studies, analysis of weight of evidence, and approaches used to identify the critical endpoints and derive No Observed Effect Levels (NOELs) to calculate margins of exposure (MOEs).

In the pharmacokinetics section, DPR concluded that oral and dermal absorption factors were 40 percent and 17 percent, respectively. Additional support needs to be provided for selection of these values. OEHHA supports setting inhalation absorption at 100%, as DPR has done for propargite.

Inhalation toxicity for all exposure durations was evaluated using an estimated NOEL from an acute lethality (LC_{50}) study. Significant uncertainties are associated with the use of lethality as an endpoint and extrapolation from short-to long-term exposure durations. Therefore, OEHHA recommends that DPR consider using route-to-route extrapolation and adopting points of departure (PODs) from the oral toxicity studies to assess longer-term exposure scenarios.

Dermal toxicity as local irritation, sensitization and systemic toxicity was evaluated based on dermal toxicity studies in rabbits, which were regarded as the most sensitive species. However, the RCD also noted that humans may be more sensitive to skin irritation under certain situations such as those that existed for nectarine workers exposed to propargite foliar residues. OEHHA concurs with the selection of the PODs for skin irritation and systemic dermal toxicity, and the application of an additional uncertainty factor (UF) of 3 for skin sensitization. However, OEHHA recommends reconsideration of interspecies differences for skin irritation, specifically the possibility that humans may be more sensitive than the most sensitive animal species tested.

The term reference concentration (RfC) was applied in three different contexts. Two of these uses [to identify an estimated threshold for dermal toxicity (e.g., page 2, second paragraph and Summary Table 1) and to identify *de minimis* cancer risk (e.g., page 57, last two sentences of the central paragraph)] are not conventional practice in human health risk assessment. OEHHA recommends that DPR retain RfC solely as a term to describe an inhalation concentration that is unlikely to cause non-cancer toxicity in humans who are exposed for a lifetime and use alternate terms to describe the other two situations. (Additional details are provided below under General Comments.)

OEHHA supports DPR's conclusion that propargite is a potential carcinogen in humans, with the potency factor based on undifferentiated sarcomas of the jejunum in Sprague-Dawley rats. For the calculation of risk, OEHHA suggests incorporation of age-sensitivity factors (ASFs) to account for increased risk of cancer due to exposure during childhood, as is the approach used by OEHHA. An example calculation is provided in an attached appendix.

OEHHA agrees that an additional uncertainty factor for pre- and postnatal sensitivity is not necessary for acute exposures because the most sensitive oral study is a developmental toxicity study. However, OEHHA is concerned about inhalation exposure and the potential for propargite to cause lung irritation and adversely affect lung development in children. Lack of experimental data in this regard represents a data gap that may warrant application of an additional uncertainty factor, and this consideration should be addressed in the RCD.

In the Risk Characterization section, aggregate MOEs were calculated using inhalation NOELs and oral NOELs based on effects in different target organs. DPR should consider revising the total MOE calculations using NOELs for the same target organs because an aggregate assessment is concerned with the total effect on a particular target organ by a chemical entering the body from multiple routes of exposure. For propargite, route-to-route extrapolation may be necessary since there is a paucity of inhalation toxicity data. Therefore, the inhalation MOE would be calculated using the POD for systemic effects from an oral study. Alternatively, aggregate MOEs can be calculated for total exposure (the sum of oral and inhalation routes) and applying a single oral POD.

OEHHA recommends that DPR evaluate the data for toxicologically significant endpoints relevant for MOE calculations using benchmark dose (BMD) modeling to determine if more appropriate PODs can be established. OEHHA also suggests that the RCD incorporate breathing rates for infants (0<2 years of age) presented in the document, *Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis* (OEHHA, 2012).

The exposure assessment section generally reflects the information from the Exposure Assessment Document (EAD). OEHHA's comments on the EAD are provided in a separate memo.

GENERAL COMMENTS

Terminology

The RCD used three different definitions for the term reference concentration (RfC) as shown below. To avoid confusion and be consistent with standard health risk assessment practice, OEHHA recommends using the first definition for the RfC and alternative nomenclature for the two other situations.

1. As defined by the U.S. EPA, an RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The units are chemical mass per unit volume of air [e.g., milligrams per cubic meter (mg/m^3) or parts per million (ppm)].

2. RfC was also used in the RCD to describe a toxicity threshold for dermal loading, leading to local or systemic effects. The units for dermal loading are chemical mass per unit skin surface area [e.g., milligrams per square centimeter of skin surface (mg/cm^2)]. This is a non-conventional use of the term RfC, and could be confusing. OEHHA recommends that DPR use a term specific to the concept, such as dermal reference concentration (RfC_{dermal}), when referring to the threshold concentration (in units of mg/cm^2) of a chemical on the skin.

3. The RCD includes a third definition of RfC that refers to an airborne concentration that equates to a 10^{-6} ("*de minimis*") cancer risk, with units of chemical mass per unit volume of air [e.g., micrograms per cubic meter ($\mu g/m^3$)]. This too is a non-conventional use of the term and may cause confusion because RfC has long been used by the U.S. EPA as the concentration in air used to characterize the non-cancer hazard of airborne contaminants. The phrase "de minimis risk concentration" (DMRC) might be more appropriate.

Points of Departure

DPR used the traditional No Observed Effect Level/Lowest Observed Effect Level (NOEL/LOEL) approach for determining the PODs for MOE calculations for propargite. OEHHA recommends that DPR evaluate toxicologically significant endpoints using the BMD modeling approach, when possible, to derive PODs.

Breathing Rates

DPR used default average breathing rates of 0.59 cubic meters per kilogram body weight per day (m^3/kg-day) for children and 0.28 m^3/kg-day for adults to estimate human equivalent exposure doses from experimental animal studies, and to calculate human exposure levels (in terms of mg/kg-day) from air concentrations. According to the RCD for chloropicrin (DPR, 2011), these breathing rates were recommended in an internal policy memorandum developed by DPR in 2000. OEHHA recommends that DPR update its policy and consider citing the breathing rates developed for the *Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document (TSD) for Exposure Assessment and Stochastic Analysis* (OEHHA, 2012). In the TSD, the mean and 95th percentile daily breathing rates for infants are 0.66 and 1.09 m^3/kg-day, respectively; for adults the corresponding values are 0.19 and 0.29 m^3/kg-day. OEHHA recommends use of the 95th percentile daily breathing rates in Tier I cancer risk assessments conducted for the Hot Spots Program (see Appendix I, page 16).

SPECIFIC COMMENTS

Route-specific Absorption Efficiencies

The oral absorption of propargite was estimated to be 40 percent based on a bioavailability study in rodents (Gay, 1994). However, the study reported that oral bioavailability was 80 percent in rats and 75 percent in mice when the area under the plasma concentration curve was extrapolated to infinity and adjusted for dose and clearance. The RCD stated that the bioavailability calculation did not take into consideration clearance rates because of a "flip-flop phenomenon." This lowered the oral bioavailability to 35.5 percent in female rats and 53.6 percent in female mice. The explanation for this phenomenon and the calculations were unclear. OEHHA recommends that DPR provide additional details on the methodology that was used to determine the oral bioavailability of propargite.

Dermal absorption of propargite was estimated to be 17 percent. Experimental data in rats (Andre et al., 1989; Chadwick, 1989a; Chadwick, 1989b; Chadwick, 1989c) were

cited to support this estimate. However, in another set of studies dermal absorption estimates ranged from 6 to 20 percent (Mizens et al. 1990; Andre et al. 1990a; Andre et al. 1990b; Andre et al. 1990c), and it is unclear why a value of 17 percent was chosen over the maximum observed absorption of 20 percent. The RCD stated the test dose used to derive the 17 percent dermal absorption value is comparable to worker exposure levels, but no data were presented to support this assertion. A reference for dermal absorption values in workers was cited on page 59 (Thongsinthusak, 1989), but it was not listed in the references section. OEHHA tentatively agrees with the dermal absorption estimate, but suggests that DPR provide additional discussion and justification for selecting 17 percent.

OEHHA supports setting inhalation absorption efficiency at 100 percent.

Inhalation Toxicity (Acute, Subchronic, and Chronic)

The RCD identified one inhalation study (Hoffman, 1992) from which PODs for inhalation exposure for all exposure durations were derived. The Hoffman (1992) study was given preference because the compound was administered by inhalation – the same route of exposure that humans are expected to experience – thus avoiding uncertainties related to route-to-route extrapolation (page 48 of the RCD).

The study consisted of a single, nose-only exposure of five male and five female rats per group to 0.31, 0.80 or 1.3 mg/L aerosolized technical grade propargite for four hours. Deaths were observed at all dose levels, with all animals at the highest concentration dying from 1 to 17 days post exposure. The most common adverse effects were reductions in body weight, clinical signs (moist rales, edema, labored breathing and anogenital stains), discoloration of the lungs, and death. Additionally, emphysema was observed in a single animal at each concentration, but this was not mentioned in the RCD. From this study, the acute LOEL was 0.31 mg/L (50 mg/kg), and an acute NOEL of 0.031 mg/L (5 mg/kg) was estimated by dividing the LOEL by a default UF of 10. OEHHA recommends that DPR include in the RCD the equations that were used to convert the exposure concentrations (mg/L) and duration (4 hours) to absorbed doses (mg/kg). The NOEL was extrapolated to 8-hour and 24-hour exposure durations to address worker and resident exposures, respectively, using Haber's Law.

The acute NOEL was extrapolated, using another UF of 10, to derive a single value for both subchronic and chronic toxicity (pages 54 and 83). The rationale for using a single UF of 10 to extrapolate from acute to chronic exposure duration was based on the similarity between lowest oral NOELs in subchronic and chronic toxicity studies in rats (pages 50-54).

OEHHA disagrees with the choice of the Hoffman (1992) study to evaluate the inhalation toxicity of propargite for intermediate and long-term exposure durations. The study was designed to establish an LC_{50} and the exposure concentrations were very high. This resulted in deaths at all dose levels. Also, it is possible that the toxicity observed was in part a non-chemical specific effect of inhaling particles, as well as irritation caused by propargite during the nose-only exposure. (There was no mention of a carrier in this study. Thus, lethality is not a useful endpoint to use in risk assessment, where the basis should be a much lower level of toxicity to extrapolate to the general public. OEHHA recommends conducting route-to-route extrapolation using results from oral toxicity studies to address inhalation toxicity for all durations. The RCD indicated that the most common systemic effect observed following exposure to propargite, regardless of route, was reduced body weight. While body weight reduction may be considered a non-specific general effect, this suggests target site/endpoint concordance. For comparison, the acute oral POD (an absorbed dose of 0.8 mg/kg-day) from Serota et al. (1983) was three-fold lower than the acute 8-hour worker inhalation POD of 2.5 mg/kg (same as absorbed dose since inhalation absorption is assumed at 100 percent), but similar to the 24-hour residential inhalation POD of 0.83 mg/kg-day (page 48).

Oral Toxicity (Acute, Subchronic, and Chronic)

DPR used NOELs from oral toxicity studies to calculate the MOEs for aggregate exposure of the general public (page 81 and Table 35). The critical acute oral NOEL (2 mg/kg-day) was based on delayed ossification of fetuses and maternal anorexia, as reported in a developmental toxicity study in rabbits (Serota et al., 1983; Table 10). The critical subchronic and chronic oral NOEL (3.8 mg/kg-day) was based on decreased body weight, as reported in a two-year feeding study in rats (Trutter, 1991; Table 12). OEHHA concurs with the selection of these oral NOELs as PODs for MOE calculations. Route-to-route extrapolation of this study may be useful for deriving an inhalation POD.

Dermal Systemic Toxicity (Acute, Subchronic, and Chronic)

There was only one identified acute dermal toxicity study that evaluated acute lethality of propargite (Kiplinger 1993). In this study, conducted in New Zealand White rabbits, vocalization, abnormal defecation, reduced appetite, scabbing and swelling around the mouth, and nose and anogenital staining were observed. However, this study was not suitable for risk assessment because only one dose level was tested. Therefore, DPR examined the subchronic dermal studies to derive the POD for acute systemic toxicity. In a 21- day dermal exposure study in rabbits conducted by Bailey (1987), no observable signs of systemic toxicity were reported during the first week of exposure at the highest dose tested (100 mg/kg-day). OEHHA concurs with the selection of the

Bailey (1987) study to evaluate acute systemic dermal toxicity and identification of 100 mg/kg-day as the POD for acute systemic toxicity resulting from dermal exposure.

Bailey (1987) also provided data for subchronic systemic toxicity resulting from dermal exposure. A NOEL of 1 mg/kg-day was identified, based on reduced body weight, increased relative kidney and liver weights, and changes in clinical chemistry and hematology values. OEHHA concurs with DPR's selection of the Bailey (1987) study as the critical study for subchronic toxicity and identification of 1 mg/kg-day as the POD.

There were no chronic dermal toxicity studies identified in the RCD. Therefore, DPR elected to use the 21-day rabbit study (Bailey, 1987) to evaluate chronic systemic dermal toxicity. The RCD stated that a subchronic-to-chronic duration uncertainty factor is not necessary because the NOELs for subchronic and chronic oral toxicity studies in rats were comparable. OEHHA concurs with DPR's evaluation of potential chronic toxicity based on subchronic dermal exposure.

Dermal Local Irritation (Acute, Subchronic, and Chronic)

To evaluate acute dermal irritation, DPR selected a 21-day rabbit study (Goldenthal, 1989) as the critical study, and examined the data for acute effects. The 21-day rabbit study by Bailey (1987) was not used because the compound was administered in acetone, which induced dermal irritation itself. In the Goldenthal (1989) study, four dose levels were tested: 2.1, 4.5, 12.5 and 28 mg/cm^2. The duration of exposure was six hours, and animals were examined for signs of dermal irritation one day after exposure. Slight to moderate erythema was observed at the lowest concentration tested. Based on these results, a LOEL of 2.1 mg/cm^2 was identified. Because the observed effect after one exposure was relatively mild compared to effects observed after 21 days of exposure, an uncertainty factor of 3 was applied to the LOEL to derive an estimated NOEL of 0.7 mg/cm^2. OEHHA agrees with the selection of the Goldenthal (1989) study and the POD derivation for acute dermal irritation.

Goldenthal (1989) also evaluated propargite for subchronic dermal irritation. A subchronic LOEL of 2.1 mg/cm^2 was identified based on moderate erythema and edema, eschar, exfoliation, atonia, desquamation, fissuring, and blanching. An uncertainty factor of 10 for LOEL-to-NOEL extrapolation was applied to derive an estimated subchronic NOEL of 0.21 mg/cm^2. OEHHA concurs with the study selection and the POD derivation for subchronic dermal irritation.

Chronic dermal exposure was not evaluated by DPR in the Exposure Assessment Document. DPR noted that the risk of dermal irritation would be maximal during the peak season of pesticide application, which lasts for several months. Therefore, DPR

concluded that the chronic exposure on a time-weighted average basis would be less than the subchronic/seasonal exposure. OEHHA concurs with this analysis and conclusion.

Dermal Toxicity: Interspecies Sensitivity

Dermal PODs (for both systemic toxicity and dermal irritation) were derived from rabbit toxicity studies. A seasonal dermal reference concentration (referred to as an RfC in the RCD) of 7 $\mu g/cm^2$ for dermal irritation was derived from a 21-day repeated exposure study (Goldenthal, 1989; page 52). However, a dislodgeable foliar residue (DFR) NOEL of 0.2 $\mu g/cm^2$ (i.e., the areal concentration of removable propargite residues on the surface of treated leaves which, based on surface-to-skin contact modeling, corresponds to a dermal concentration of 1.2 $\mu g/cm^2$ on the hands and forearms) was identified following several outbreaks of dermal irritation, particularly among nectarine harvesters (page 84). The estimated dermal loading from the nectarine harvester study was about 6-fold lower (7 $\mu g/cm^2$ *vs.* 1.2 $\mu g/cm^2$) than the seasonal dermal reference concentration derived from the Goldenthal (1989) study, suggesting that humans may be significantly more sensitive to propargite-induced dermal irritation than rabbits. For this reason, OEHHA recommends that DPR include an additional UF of 10 to account for interspecies differences in sensitivity to propargite-induced dermal irritation between rabbits and humans. Furthermore, additional information on the nectarine harvester studys– if available – should be included in the toxicology profile of the RCD.

The RCD cited Griem (2008) in the discussion of the role of sensitizers in quantitative risk assessment. Dermal sensitization is often determined via the local lymph node assay (LLNA) in animals, and it has been suggested that EC3 values (effective concentrations inducing a stimulation index of 3) derived from LLNA may serve as surrogate NOELs. However, the LLNA was not conducted for propargite so EC3 values were not available. The results from standard sensitization tests in guinea pigs, using the Buehler or Maximization Test, were equivocal (Tables 1-3). Thus, it is unclear whether propargite truly is a dermal sensitizer. Griem (2008) recommended a number of uncertainty factors when conducting quantitative risk assessment for sensitizers: 3 for interspecies extrapolation, 10 for intraspecies variability, 1-10 for a matrix factor, and 1-10 for a use factor. Because propargite's status as a sensitizer in unclear, OEHHA supports DPR's decision to include an additional uncertainty factor of 3 for dermal irritation to protect against dermal sensitization, in addition to the recommended factor of 10 for increased sensitivity of humans relative to guinea pigs to skin irritation from propargite.

Developmental Toxicity

Two rat (Knickerbocker, 1 979; Schardein, 1990) and two rabbit (Serota et al., 1 983; Schardein, 1989) teratology studies were reviewed in the RCD. Developmental effects included skeletal variations related to delayed ossification (Knickerbocker, 1 979; Serota et al., 1983), abortions (Schardein, 1989), reduced fetal viability (Serota et al., 1983; Schardein, 1990), fused sternebrae (Serota et al., 1983; Schardein, 1989), and reduced pup weight (Serota et al., 1983). Each study design was described, and maternal and developmental NOELs were identified. OEHHA notes that a developmental NOEL, 6 mg/kg-day based o

Page 44 of the RCD stated that the abortions reported at 4, 6, and 8, mg/kg-day in the Schardein (1989) study are not related to treatment. From OEHHA's perspective, not enough information was provided to justify the decision to discount the incidences of abortion in this study. Furthermore, it is unclear whether, the abortion data provided in rable 9 (page 45) include the abortions that DPR deemed unrelated to propargite exposure or represent the actual data from the study. OHHA does not agree with the abortions at 4-8 mg/kg-day in the Schardein (1989) study were not considered treatment related. OEHHA does agree with the NOELS that were identified in the other three developmental toxicity studies.

Reproductive Toxicity

Two rat reproductive toxicity studies were reviewed in the RCD (Kehoe, 1 990; York, 1992). The primary adverse effect observed in the studies was reduced body weight in both the dams and pups. There were no evident effects on mating, fertility, or gestation. A reproductive NOEL of 4 mg/kg-day was identified based on postnatal growth reduction in pups. A maternal NOEL of 4 mg/kg-day was identified based on reduced body weights. OEHHA

The RCD also included discussion of a second investigation by York (1992) that examined the roles of indirect propargite exposure on pups through nursing. This was a complex cross-fostering study with multiple experimental groups. The investigators concluded that reduced pup weight was due to maternal toxicity and direct propargite exposure through diet, and that indirect exposure through nursing was inconsequential. However, the narrative did not mention when the pups started feeding on a propargite-supplemented diet, so it is difficult to determine exactly when this exposure pathway (i.e., direct dietary ingestion) became relevant. Reduced pup weights at

nursing behavior. Additionally, reductions in pup weight may have been mediated through earlier maternal factors such as the presence of the chemicals in the milk, reduced milk production, or effects on lactational (nursing) behavior. OEHHA concurs with DPR's assessment that dam-mediated effects cannot be ruled out in the York (1992) cross-fostering study. This sub-section of the RCD appears to provide additional support for the conclusion that propargite is unlikely to cause reproductive toxicity, but the health risk implications of the results of this study should be clarified.

Risk Characterization: Pre- and Post-natal Toxicity

The RCD stated that "there is no increased susceptibility in infants and children to propargite" because developmental NOELs were equal to or greater than maternal NOELs (page 91). However, a number of fetal effects (increased abortions, increased resorptions, reduced fetal viability, delayed ossification, malaligned or fused sternebrae, hydrocephaly, and reduced body weights) were identified in animal studies. In the Knickerbocker (1979) rat study, the developmental NOEL was 6 mg/kg-day whereas the maternal NOEL was 25 mg/kg-day. This suggests that the fetus is more sensitive to propargite than the dam. Additionally, in the Schardein (1989) rabbit study, the basis for discounting the elevated incidences of abortions at 4-8 mg/kg-day is not clearly explained, and therefore it is unclear whether the developmental NOEL should be 2 mg/kg-day or 8 mg/kg-day. OEHHA recommends that DPR address these issues before concluding that infants and children are not more sensitive than adults to propargite exposure.

Nevertheless, an additional uncertainty factor for fetal sensitivity is probably not needed for acute exposures. Should DPR elect to conduct route-to-route extrapolation (oral to inhalation) to assess inhalation exposure, the lowest acute oral NOEL (2.0 mg/kg-day, 0.8 mg/kg-day absorbed, based on Serota et al., 1983) is from a developmental toxicity study, and therefore addresses prenatal toxicity. This acute absorbed oral NOEL is very close to the 24-hour acute inhalation NOEL of 0.83 mg/kg derived from the Hoffman (1992) study. The oral NOEL of 3.8 mg/kg-day identified in the Trutter (1991) study appears to be appropriate for adults seasonally or chronically exposed to propargite.

OEHHA has concern that inhalation toxicity and lung irritation have not been thoroughly examined, particularly in young animals. As noted in the RCD, a single acute inhalation study (Hoffman, 1992) was conducted on adult rats using very high concentrations of aerosolized propargite. Inhalation studies of longer duration have not been conducted. Since humans are expected to be exposed to propargite by inhalation, this represents a significant data gap. Additionally, the lungs of young children are not fully developed. Humans form 80% of their alveoli postnatally (Plopper and Fanucchi, 2004), with alveoli

continuing to develop to at least the age of eight (Boyden, 1971). Therefore, OEHHA recommends that DPR consider incorporating an additional uncertainty factor to address lack of toxicity information to assess longer-term inhalation exposures during childhood.

Genotoxicity

OEHHA supports the conclusion in the RCD that the available genotoxicity data for propargite are negative. However, the RCD should note that there are no oxidative DNA damage data available for propargite. The *Salmonella* mutation assays cited did not use test strains TA102 or TA104, both of which are designed to be sensitive to chemicals which induce oxidative DNA damage. Additionally, no COMET assay or oxidative DNA adduct data exist for propargite. The one DNA damage assay available for propargite measured unscheduled DNA synthesis (UDS) in rat hepatocytes, but this assay is relatively insensitive. Therefore, while the genotoxicity data are generally negative, the lack of oxidative DNA damage data for propargite should probably be noted in the RCD.

Oncogenicity

The key oncogenicity study was conducted by Trutter (1991), who reported an increase in sarcomas of the jejunum in Sprague-Dawley rats chronically exposed to propargite. Cancer potency estimates [2.4×10^{-2} $(mg/kg\text{-}day)^{-1}$ for the maximum likelihood estimate (MLE) and 3.4×10^{-2} $(mg/kg\text{-}day)^{-1}$ for the 95 percent upper bound] were determined using U.S. EPA's BMDS 2.2 software, multistage-cancer model (page 57 of the RCD). OEHHA verified these calculations and concurs with the selection of this study as the basis for cancer potency estimates.

Supporting evidence of carcinogenicity was provided by a second lifetime study (FDRL, 1966) that reported an increase in intestinal sarcomas in Food, Drug and Research Laboratories (FDRL; Wistar-derived) rats. Evaluation of the sarcoma incidence (all types) demonstrates a significant positive trend test and a near-significant difference when compared to controls ($p = 0.061$, one-tailed Fisher exact test). If the male and female sarcoma incidence data are combined, the difference is significant ($p = 0.024$, one-tailed Fisher exact test) compared to controls. This analysis suggests that propargite is carcinogenic in Wistar rats and adds to the weight of evidence for propargite carcinogenicity. Furthermore, the statistically significant increase in cell proliferation in the outer longitudinal layer of the tunica muscularis of female Wistar rats that were fed propa

cancer bioassay. OEHHA suggests that a more detailed discussion of the Wistar rat studies be provided in the RCD.

Cox and Re (1979) conducted a cancer bioassay of propargite in CD-1 mice. The exposure durations were 12 and 18 months, and this reduced the sensitivity of this study since they are less than the mouse experimental lifetime (2 years). OEHHA recommends that reduced sensitivity of this study should be noted in the study description in the RCD.

OEHHA suggests that DPR incorporate age sensitivity factors (ASFs) in the calculation of cancer risks to account for enhanced juvenile sensitivity to carcinogens. An example of such an analysis, based on OEHHA's Hot Spots risk assessment guidelines (OEHHA, 2012), is included in Appendix I. This example calculation incorporates ASFs as well as age group-specific 95th percentile point estimates of breathing rates.

Aggregate Exposure Toxicity

The potential for aggregate exposure of agricultural workers (8 hours of work time; diet, drinking water and residential ambient air) was discussed on page 69 of the RCD. Since occupational exposure represented 80 to 99.9 percent of the estimated aggregate exposure, MOEs for aggregate exposure of workers were no

Aggregate exposure estimates were also presented for the general public (in the diet, drinking water, and application site air; Tables 22, 34 and 35) for acute (1 hour and 24 hours), seasonal and chronic exposure durations. The risk for the inhalation pathway was evaluated using NOELs derived from an acute inhalation toxicity study (Hoffman, 1992). The oral pathway was evaluated using NOELs from oral toxicity studies (Serota et al., 1983; Trutter, 1991). As discussed earlier, the endpoints for these NOELs are different. OEHHA recommends that the aggregate MOEs for the general public be calculated using PODs derived from oral toxicity studies because of concerns about the applicab

Margin of Exposure (MOE) Calculations

OEHHA concurs with DPR that an MOE of 100 is sufficient for dermal systemic effects and inhalation effects in adults at

The RCD stated that a MOE of 10 is considered adequate for dermal irritation because DPR concluded that rabbits are more sensitive than humans to propargite, and an additional interspecies extrapolation UF of 10 is unnecessary. However, a dermal irritation NOEL derived from nectarine harvesters suggests that humans may be more sensitive than rabbits to propargite, and OEHHA suggests that the additional UF of 10 for interspecies differences be adopted. The RCD also stated that an uncertainty factor of 3 should be applied to account for dermal sensitization. Therefore, OEHHA recommends that an MOE of 300 is the appropriate benchmark to gauge adequate human health protection from dermal irritation.

OEHHA also suggests that DPR consider an additional UF for inhalation sensitivity when calculating MOEs for children because propargite is a pulmonary irritant and the only available inhalation toxicity data are for acute, high dose exposures in adult animals. OEHHA regards the lack of data characterizing the adverse effects of longer-term inhalation exposure and exposure in young animals as a gap in the toxicity database. In general, data gaps of this magnitude are addressed by incorporating an additional UF in the risk appraisal process.

EDITORAL COMMENTS

DPR calculated RfCs for children and adults by adjusting the POD from a laboratory animal study with a breathing rate ratio to account for the difference in breathing rates between rats and humans, and dividing by a default uncertainty factor of 100. Actual formulae and example calculations should be included in the RCD.

Page 2, 1st paragraph, last sentence: The words "for adult" associated with 0.18 µg/L are missing.

Summary Table 1 (page 4) and Table 13 (page 58) summarized critical endpoints, NOELs and reference concentrations for propargite. These tables would be more informative if they included absorbed doses and a citation (author, year) for each key study. They should also include the oral NOELs used for assessing aggregate exposure for the general public (see Table 23 on page 71 and Table 35 on page 82). Summary Table 1 stated that the "RfC" for acute dermal local effects was 70 µg/cm^2, but Table 13 and page 49 in the text indicated it was 23 µg/cm^2. Similarly, the seasonal "RfC" for this endpoint was given in Summary Table 1 as 21 µg/cm^2, whereas Table 13 and page 52 (text) indicated it was 7 µg/cm^2. In both tables, the header for the second column should indicate that the NOELs are estimated or calculated values, and the header for the third col

Page 46: OEHHA noted a slight discrepancy in the Hazard Identification Section. Page 54 of the RCD indicated that the critical NOEL used to evaluate subchronic residential inhalation exposure, 96 µg/kg-day, was also used to evaluate chronic residential inhalation exposure. Similarly, the subchronic 8-hour inhalation NOEL, 288 µg/kg-day, was also used to evaluate chronic occupational inhalation exposure. However, the subchronic NOELs reported on page 54 do not match the values reported at the bottom of page 50 (83 and 250 µg/kg-day for residential and occupational

Table 10: NOEL and LOEL column headings indicated that doses were in units of mg/kg. For studies with multiple exposures, the units should be mg/kg-day.

Page 62: The last line was just a single word. The beginning of the last sentence needs to be connected to the rest of the same sentence on page 63.

Page 68, 2nd paragraph: DPR stated "An average air level of 0.03 µg/m^3 from all the sampling sites around the application site during the 3 days of monitoring were [sic] used for estimating seasonal exposure". However, footnote (c) of Table 22 listed a mean concentration of 0.3 µg/m^3 for seasonal exposure, and the propargite EAD (DPR, 2012) indicated a concentration of 1.0 µg/m^3 in footnote (d) of Table 23. The calculations in this section of the RCD suggest that the correct value for seasonal exposures is 1.0 µg/m^3. The text in this section and the Table 22 footnote should be corrected to reflect this.

Page 71: The combined MOE equation is incorrect. It should be:

$$MOE_{combined} = 1/[(1/MOE_1) + (1/MOE_2) + (1/MOE_3)]$$

The results of the calculations appear to be correct.

Page 81: According to the text on this page, the 24-hour acute MOE for adults should be 1,300 instead of 2,300 as indicated in Table 34.

Page 82, footnote a: It appears that the absorbed oral dose should be 1,520 µg/kg-day instead of 1,540 µg/kg-day since the NOEL identified in the Trutter (1991) study was 3.8 mg/kg-day and the oral absorption factor was assumed to be 40 percent (page 16).

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APPENDIX I. – Example Cancer Risk Calculation with Age Sensitivity Factors

The following is an example of cancer risk calculations that include Age Sensitivity Factors (ASFs) to account for enhanced juvenile sensitivity to carcinogens. The calculations also incorporate age group-specific 95th percentile point estimates of daily breathing rates.

In the 2012 Technical Support Document (TSD) for the Air Toxics Hot Spots program, OEHHA included daily breathing rate (BR) point estimates for several age ranges and described the use of Age Sensitivity Factors (ASFs) for estimating the increased risk of cancer due to increased potency from exposure early in life (see OEHHA, 2009 for more detailed explanation of Age Sensitivity Factors). For Tier I assessments, OEHHA recommends using the 95th percentile long-term daily breathing rates of 0.29, 1.09, 0.745 and 0.29 m^3/kg-day (Table 3.1 in the TSD) for third trimester, ages 0<2, 2<16 year and 16-70 years, respectively. In addition, the Hot Spots program applies ASFs of 10, 3, and 1 for the age groups third trimester<2 years, 2<16 years and 16<70 years (Chapter 11 in the TSD), respectively. The following example uses ASFs and 95th percentile breathing rates in the calculation of inhalation cancer risk

The OEHHA algorithms for estimating dose and cancer risk by the inhalation route are as follows:

$$DOSE_{air} = C_{air} \times [BR/BW] \times A \times EF \times (1 \times 10^{-6})$$

where:

$DOSE_{air}$ = dose by inhalation (mg/kg BW-day)
C_{air} = concentration in air (µg/m^3)
[BR/BW] = daily breathing rate normalized to body weight (L/kg BW-day)
A = inhalation absorption factor, if applicable (default = 1)
EF = exposure frequency (days/365 days; default = 365/365 = 1)
1×10^{-6} = conversion factors (µg to mg, L to m^3)
and

$$RISK_{air(\text{ age group x})} = DOSE_{air\,(\text{age group x})} \times CPF \times ASF_{(\text{age group x})} \times ED/AT$$

In order to accommodate the age sensitivity factors, cancer risk is calculated for each age group separately and then summed.

$$RISK_{air\,(\text{lifetime})} = RISK_{air\,(\text{3rd trimester})} + RISK_{air\,(0<2\text{ yrs})} + RISK_{air\,(2<16\text{ yrs})} + RISK_{air\,(16\text{-}70\text{yrs})}$$

If the seasonal air concentration is adjusted to an annual concentration (1.0 µg/m^3÷3, where the growing season is assumed to be 4 of 12 months, Table 22 of RCD), then the

following inhalation cancer risks can be derived for the age groups aligned with the ASFs and summed for a lifetime (70 year) cancer risk:

Bystander Inhalation Cancer Risk Estimates Incorporating ASFs

$RISK_{air\ (3rd\ trimester)}$ = (0.33 ug/m^3 x 0.29m^3/kg-day) x 8.4 x 10^{-5} (ug/kg-day)$^{-1}$ (10) (0.25/70)
= 2.9xx10^{-7}

$RISK_{air\ (0<2yrs)}$ = (0.33 ug/m^3 x 1.09 m^3/kg-d) x 8.4 x 10^{-5} (ug/kg-day)$^{-1}$ (10) (2/70)
= 8.63 x 10^{-6}

$RISK_{air(2<16yrs)}$ = (0.33 ug/m^3 x 0.745 m^3/kg-d) x 8.4 x 10^{-5} (ug/kg-day)$^{-1}$ (3) (14/70)
= 1.24 x 10^{5}

$RISK_{air\ (16-70yrs)}$ = (0.33 ug/m^3 x 0.29 m^3/kg-d) x 8.4 x 10^{-5} (ug/kg-day)$^{-1}$ (1) (54/70)
= 6.2 x 10-^{6}

$RISK_{air\ (lifetime)}$ = 2.75 x 10^{-5}

This lifetime risk of 2.75x10^{-5} is about 3-fold higher than the 7.8x10^{-6} risk calculated for adults only in the RCD (page 81). This higher estimated risk would in turn result in a lower estimated exposure level associated with a 10^{-6} cancer risk (termed inhalation RfC in the RCD).