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PREFACE

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

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

This report is a peer review of the draft RCD (dated and received on August 31, 2015) provided by DPR for the pesticide 1,3-dichloropropene (1,3-D). The exposure assessment was incorporated into the RCD document.

This peer review report has three parts:

I. Summary of Review
II. Response to Charge Questions, provided by DPR
III. Detailed Comments on charge questions and additional comments.

Several risk assessment and exposure assessment documents for 1,3-D have been published by DPR over the last 20 years, although the draft RCD currently being reviewed is the first complete RCD undergoing peer review by OEHHA. The previously published documents include a 1994 human exposure assessment focused on non-occupational inhalation, a 1997 human health risk assessment focused on the exposure under the permit conditions proposed for the 1994-1995 growing season, and a 2012 document on environmental fate. There has been no dietary exposure assessment as the only established tolerance has been in/on grapes in established vineyards.
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I. SUMMARY OF REVIEW

This report presents the review by the Office of Environmental Health Assessment (OEHHA) on the Department of Pesticide Regulation (DPR) draft Risk Characterization Document (RCD) for 1,3-dichloropropene (1,3-D), a widely used soil fumigant (DPR, 2015). The draft RCD characterizes the health risks from 1,3-D associated with inhalation exposure of workers, bystanders (occupational and residential), and the general public. It evaluates acute, subchronic, and chronic non-cancer health effects as well as cancer risks to these population groups. Overall, we find the document is well-written and well organized with the information presented in a logical and coherent manner.

Our principal comments are summarized below. Discussion of these comments and additional comments are provided in Section III Detailed Comments of this report.

A. Hazard Identification and Risk Characterization

1. Non-cancer endpoint selection and point of departure determination

- OEHHA agrees with the critical endpoints selected for acute toxicity (body weight reduction), subchronic toxicity (respiratory epithelial hyperplasia), and chronic toxicity (respiratory epithelial hyperplasia).

- OEHHA recommends the use of benchmark dose (BMD) modeling for all dose-response analysis to derive the point of departure (POD). Use of the default No-Observed-Effect Level (NOEL)/Lowest-Observed-Effect Level (LOEL) approach should only occur when the data are not amenable to BMD modeling. This is consistent with the OEHHA Risk Assessment Guidelines and both the U.S. Environmental Protection Agency (US EPA) approach and the National Research Council (NRC) recommendations to DPR (NRC, 2015) for dose-response analysis. In the draft RCD, the advantages of BMD modeling were discussed extensively, but BMD modeling was only used to derive the POD for acute toxicity. The PODs for subchronic and chronic durations were based on the NOELs, and the justification was that they were experimentally determined. OEHHA disagrees with the rationale and recommends consistent use of BMD modeling as the preferred approach.

- For short-term exposure, the draft RCD identified reduction in body weight as the critical acute health effect and determined a POD of 49 parts per million (ppm) based on a benchmark response (BMR) of one standard deviation (1 SD). OEHHA agrees with this determination.
For subchronic and chronic exposures, instead of using the NOELs as the PODs, OEHHA suggests BMD modeling with a BMR of 10% for the respiratory epithelial hyperplasia observed in the test animals for both durations. The default value for BMR is 5%; OEHHA suggests 10% because the effects are considered mild and did not worsen with increased exposure duration.

2. Carcinogenicity identification and cancer potency determination

- OEHHA agrees with the conclusion that 1,3-D is a carcinogen based on evidence from multiple studies with experimental animals. This conclusion is consistent with those of US EPA and the International Agency for Research on Cancer (IARC). 1,3-D is listed under Proposition 65 as a carcinogen.

- OEHHA concurs that 1,3-D is genotoxic and DPR provided strong evidence supporting a non-threshold mechanism approach to evaluate lung (bronchioalveolar) tumors found in mice after inhalation exposure. However, OEHHA disagrees that the lung tumor in mice was a portal of entry effect. OEHHA considers 1,3-D to be a systemic carcinogen because this tumor type was also found in the National Toxicology Program (NTP) gavage study in another strain of mice.

- OEHHA has several recommendations regarding the calculation of the potency of 1,3-D. First, count the number of animals at risk based on when the first tumor was found, instead of using an arbitrary cut-off of animals alive at one year, to determine the denominator for tumor incidence. Second, conduct a more comprehensive evaluation of tumor findings not only in test animals exposed through the inhalation route but also in those exposed through the oral routes to ensure the highest potency is used to estimate human cancer risk. And third, perform multisite tumor analysis when appropriate.

3. Interspecies extrapolation

- OEHHA supports the use of the Regional Gas Dose Ratio (RGDR) approach to convert doses in animal inhalation experiments to human equivalent concentrations (HEC) for non-cancer effects.

- OEHHA disagrees with the reduction of the intraspecies pharmacokinetic uncertainty factor (UF) from a value of \(\sqrt{10}\) to 1 for all effects, because the RGDR approach does not consider the role of metabolism and excretion. Thus, OEHHA recommends that DPR retains the interspecies pharmacokinetic UF at a value of 2 for systemic effects. A value of 1 is appropriate for a portal of entry effect.

- For the lung tumors found in mice, OEHHA recommends the use of the body weight scaled to the \(\frac{3}{4}\) power to calculate human potency, which is standard practice and is meant to account for toxicokinetic differences across species including metabolism and excretion. This approach results in an approximate 24-
fold higher human cancer potency compared to that estimated using the RDGR for portal of entry effect as the interspecies scaling factor. As noted above, OEHHA disagrees that the lung cancer is strictly a portal of entry effect.

4. Intraspecies variation and sensitive population

- For non-cancer effects, the draft RCD has an additional UF of 3 to protect children. OEHHA recommends DPR extends the protection to other sensitive populations. OEHHA uses a default UF of 10 for intraspecies pharmacokinetic variability, which accounts for subpopulations such as children, pregnant women, and the elderly possibly being more sensitive than the general population to the toxicity of a chemical. 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).

- For residential lifetime exposure, OEHHA recommends the cancer risk calculation to include age-sensitivity factors (see OEHHA, 2009). The inclusion of these factors will increase the estimated cancer risk by three-fold.

5. Risk characterization

- OEHHA recommends a re-evaluation of the target margin of exposure (MOE)\(^1\) designated by age-adults or children - to consider the toxicity type and population variation in response due to pharmacokinetic and pharmacodynamics differences. OEHHA suggests target MOE values of 100 for local effects and 200 for systemic effects.

OEHHA agrees with the use of the *de minimus* risk of \(1 \times 10^{-6}\) as the target to compare calculated human cancer risks.

B. Exposure Assessment

1. Occupational Exposure

- The pesticide illness data revealed that workers exposed while maintaining or adjusting equipment represented approximately 8% of all 1,3-D illness cases. The draft RCD does not consider this particular exposure scenario even though use of 1,3-D routinely requires this type of preventative maintenance. OEHHA recommends that the draft RCD address this exposure scenario.

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\(^1\) DPR characterized non-cancer risk resulting from 1,3-D exposure by comparing the human exposure with the MOEs. MOE values are calculated by dividing the POD by the human exposure dose, or air concentration. DPR calculated target MOEs based on UFs chosen.
When chloropicrin estimates were used to derive the exposure for applicators and tarp removers, it was not clear if the corresponding experimental variance from each individual data set was also taken into account.

OEHHA generally concurs with use of chloropicrin as a surrogate compound for scenarios where 1,3-D data are not available. However, we recommend that when estimates are derived from multiple data sets, the experimental variability from each data set be appropriately addressed. For example, DPR could identify the major source of uncertainty/variability and deal with it quantitatively. Other sources could be treated qualitatively.

Exposure levels estimated for the applicator scenarios as well as the tarp remover scenarios were based on application method-specific ratios from the chloropicrin exposure data. The underlying assumption is that chloropicrin and 1,3-D behave similarly (in terms of emission rate from soil and dispersion in air) in all these situations, but no evidence or justification to support this assumption was presented.

OEHHA recommends including additional physical and chemical property data for chloropicrin to allow direct comparison to the data for 1,3-D. In addition, the assumptions and methodology used for the chloropicrin-based exposure estimates should be clearly stated and example calculations should be provided. Supporting literature references should be included.

OEHHA also recommends adding adjustment factors for the chloropicrin-based estimates in order to address the potential for underestimating exposure. There are data from field studies indicating that the actual emission rate of 1,3-D could be higher than that extrapolated from chloropicrin measurements, following tarp cutting. This is because 1,3-D is less reactive than chloropicrin and has a longer half-life in soil. We suggest that DPR review existing field studies that directly compare the environmental fate of chloropicrin and 1,3-D, and incorporate this information into the discussion of the uncertainties resulting from this approach.

The draft RCD only used four of the five observations in estimating the 95th percentile exposure level for the key applicator scenario (shallow shank application without tarp). This resulted in reducing the estimated exposure variability from a range of 100-fold to just 10-fold. OEHHA recommends that the draft RCD provide justification for excluding the observation. The omitted data point was not subjected to any outlier analysis and appropriate justification was not provided for excluding this data point in the analysis.

For the applicator shallow shank-no tarp scenario, calculation of the 95th percentile exposure estimate requires the use of the standard deviation of the data set.
OEHHA recommends that DPR reconsider the selection of the algorithm used to calculate the standard deviation. Since a limited data set was used to estimate exposure for the larger population of workers who use this application method, it would be more appropriate for DPR to calculate the sample standard deviation.

2. Residential Exposure

- In many of the residential bystander scenarios, the presence of a 100-foot buffer zone was factored into the exposure calculations. However, it is not clear whether there are scenarios where a bystander would be exposed to 1,3-D at distances less than 100 feet from the site of application. Information on the minimum buffer zone size for each type of product and for the major application methods should be included.

For residential bystanders, OEHHA agrees with DPR that summation of exposures from both nearby applications and ambient sources is appropriate.

- The residential bystander ambient lifetime exposure estimates were derived from multi-factorial inputs, Gaussian air dispersion modelling and stochastic analysis, using two exposure models, High-End Exposure version 5, Crystal Ball (HEE5CB) and Monte Carlo Annual-Based Lifetime Exposure (MCABLE), to provide a range of exposure estimates.

OEHHA recommends that DPR use the high mobility estimates from the HEE5CB model. Since the MCABLE model has not undergone external scientific peer review, the reliability and accuracy of its outputs are not known.

Furthermore, OEHHA recommends that exposure for several age groups (women in their third trimester of pregnancy, birth to 2 years old, 2 years to 16 years old and adults 16 to 70 years old) should be estimated separately to allow for the appropriate application of age-sensitivity factors in the calculation of cancer risk.

II. RESPONSE TO CHARGE QUESTIONS

DPR asked OEHHA to address charge questions in our peer review of the risk assessment. The answers provided in this section are purposely brief with more in-depth discussion of these answers and OEHHA’s other comments in Section III, Detailed Comments.

A. Hazard Identification and Risk Characterization

Question 1: "Use of body weight decrement as a critical driver in the acute risk assessment of 1,3-D was accompanied by significant uncertainty with regard to whether
the observed weight decrements were of sufficient adversity. Please comment on whether DPR’s Human Health Assessment Branch (DPR-HHAB) was correct to base the acute 1,3-D health assessment on bodyweight decrements.”

**Answer**: OEHHA agrees with the use of body weight decrements as the critical endpoint for assessing acute exposure.

**Question 2**: “The effect of 1,3-D on body weight was assumed to be systemic in nature, implying that it had to be absorbed into the blood and distributed throughout the body before it could cause the effect...In light of these considerations, please comment on whether the assumption of a systemic mode of action is justified.”

**Answer**: OEHHA agrees that body weight reduction is a systemic effect. Many 1,3-D studies administered by other routes of exposure also resulted in reduction of body weight.

**Question 3**: “In view of the uncertainties regarding the assumption of a systemic mode of action, please comment on whether it is justified to reduce the 3x pharmacokinetic uncertainty factor to 1x because the RGDR approach was taken.”

**Answer**: OEHHA disagrees that the UF should be reduced to a value of one. The pharmacokinetic UF for interspecies extrapolation should be a value of 2 when using the RGDR approach. When assuming a systemic mode of action, local metabolism as well as systemic metabolism may affect toxicity and need to be accounted for, beyond regional lung differences.

**Question 4**: “The critical chronic NOEL of 5 ppm (hyperplasia of the murine nasal epithelium at 20 ppm) was adjusted to human equivalent concentrations of 0.16 and 0.49 ppm for non-occupational and occupational scenarios, respectively. The RGDR of 0.198 used to make this conversion was based on an extrathoracic portal of entry mode of action...Please comment on whether it is appropriate to base the chronic health assessment on the relatively slight extrathoracic effects (resulting in lower HECs) than on the systemic effects.”

**Answer**: OEHHA agrees with the choice of using portal of entry respiratory tract effects as the chronic toxicity endpoint because changes in the nasal epithelial histopathology, while mild, have been observed in numerous other studies and are considered an adverse effect. Since portal of entry effects resulted in lower HECs, they are protective of systemic effects and appropriate for risk assessment. This conclusion is still valid when OEHHA’s recommended interspecies UF of 2 was applied toward the bladder effect.

**Question 5**: “There are reasons to question the multistage linear extrapolation approach for inhaled 1,3-D-induced lung tumors. Most importantly, the incidence curve for bronchioalveolar adenomas---9/49, 6/50, 13/49 and 22/50 at 0, 5, 20 and 60 ppm---

1,3-Dichloropropene
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suggests the existence of an *effective* threshold for tumor production. In this view, very low concentrations of 1,3-D would *not* induce tumors since the organism has the presumed capacity to detoxify the chemical through metabolism and/or excretion. Please comment on whether it is appropriate for DPR-HHAB to use a linear extrapolation model to characterize the oncogenic risk of 1,3-D.”

**Answer:** OEHHA concurs that 1,3-D is a genotoxicant and a linear extrapolation model to characterize the oncogenic risk is appropriate. There is insufficient mechanistic evidence to support a threshold mode of action for lung tumors.

**B. Exposure Assessment**

**Handler Exposure**

**Question 1:** Please comment on the surrogate approach used to generate the exposure estimates for the following handler scenarios:

a. applicator (shallow shank w/ tarp)
b. applicator (drip w/ tarp)
c. applicator (drip w/o tarp)
d. applicator (hand-wand)
e. tarp remover

**Answer:** OEHHA generally concurs with use of chloropicrin as a surrogate compound for scenarios where 1,3-D data are not available. However, we have concerns regarding the following issues:

- Occupational estimates from multiple data sources did not include experimental variability from each source. OEHHA recommends that experimental variability from multiple data sets should be appropriately addressed. For example, DPR could identify the major source of uncertainty/variability and deal with it quantitatively. Other sources could be treated qualitatively.
- There is a lack of supporting evidence for the assumption that the physical and chemical properties of chloropicrin and 1,3-D are similar enough that their fate in the environment is comparable. The exposure estimates for these scenarios could be underestimated because of differences in the volatility and persistence of the two compounds. OEHHA recommends that DPR (1) evaluate how differences in the chemical and physical properties of chloropicrin and 1,3-D may affect their environmental fate, which in turn may impact 1,3-D exposure estimates, and (2) if necessary, add an adjustment factor to account for the potential underestimation of 1,3-D exposure.
Residential Bystander Exposure

**Question 1**: Two human stochastic exposure assessment models were used to evaluate the lifetime exposure to 1,3-D by individuals residing in a high 1,3-D use area: Monte Carlo Annual-Based Lifetime Exposure model (MCABLE) and High-End Exposure version 5, Crystal Ball (HEE5CB). Please comment on the modeling approach taken in this risk assessment to characterize the exposure and cancer risk estimates of 1,3-D.

**Answer**: OEHHA recommends that DPR use the high mobility exposure estimates from the HEE5CB. The MCABLE model is more complex and is less transparent than HEE5CB. Furthermore, MCABLE has not undergone external scientific peer review and the scientific validity of its assumptions for duration and mobility is uncertain.

- In comparing the two models, the HEE5CB exposure estimates were higher than MCABLE estimates. The MCABLE estimate incorporated all 100 years of the simulated annual air concentrations into the final exposure calculations, which may result in underprediction. In contrast, HEE5CB used a 31 year subset of all the simulated annual air concentrations to calculate the exposure estimates in order to avoid underestimating exposure.

- Regarding lifetime exposure, OEHHA recommends that exposure for several age groups (women in their third trimester of pregnancy, birth to 2 years old, 2 years to 16 years old and adults age 16 to 70 years old) should be estimated separately. This allows for the appropriate application of age-sensitivity factors in the calculation of cancer risk.

**Question 2**: Please comment on the approaches used to estimate the seasonal and annual 1,3-D air concentrations for the shallow shank, deep shank, and drip application methods.

**Answer**: The assumptions and methods used to calculate the seasonal air concentration (SAC) and annual air concentration (AAC) seem reasonable. OEHHA agrees that summation of exposures from both nearby applications and ambient sources is appropriate when estimating residential bystander exposure.

In many of the residential bystander scenarios, the presence of a 100-foot buffer zone was factored into the exposure estimates. However, it is not clear whether there are scenarios where a bystander would be exposed to 1,3-D at a distance less than the 100-foot label requirement.

OEHHA recommends that the draft RCD should include additional information on the minimum buffer zone size for each type of product and for the major application methods. This concern about the buffer zone also applies to short-term exposure.
III. DETAILED COMMENTS

A. Introduction

1,3-dichloropropene (1,3-D) (CAS # 542-75-6, molecular formula $\text{C}_3\text{H}_4\text{Cl}_2$) is one of the most widely used fumigants in California. It is currently used under the trade name Telone® or Telone II®. Many of the formulations contain chloropicrin, also a fumigant, as much as 80% of the formulation by weight (DPR, 2015). State-wide use of 1,3-D has increased four-fold between 1998 and 2012 and reached 12.9 million pounds in 2013. It is used as a pre-plant control for parasitic nematodes and other soil pests on a wide variety of crops and ornamentals. 1,3-D is a liquid that is a mixture of cis- and trans-isomers. It is miscible in most organic solvents and is volatile.


The following sections present detailed discussion of OEHHA’s answers to charge questions, principal comments presented in Sections I and II, as well as additional comments for the Draft RCD.

1. Product and Formulations and Uses

1,3-D is often formulated as a mixture containing chloropicrin (see Table 1). According to 2013 Pesticide Usage Report (PUR) data, chloropicrin accounted for 43% of the weight of the 1,3-D formulations in use at that time. Thus, OEHHA is concerned about the co-exposure of workers and residents to chloropicrin, as discussed in later sections of this report.

Table 1. 2013 California Pesticide Usage Report (PUR) data for 1,3-D formulations, alone and with chloropicrin

<table>
<thead>
<tr>
<th>1,3-D Products</th>
<th>Product Composition</th>
<th>Product (million lbs)</th>
<th>1,3-D (million lbs)</th>
<th>Chloropicrin (million lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telone II</td>
<td>~ 97.3% 1,3-D</td>
<td>9.94</td>
<td>9.67</td>
<td>none</td>
</tr>
<tr>
<td>Pic-Chlor 60</td>
<td>~38% 1,3-D + ~59% CP</td>
<td>6.24</td>
<td>2.39</td>
<td>3.65</td>
</tr>
<tr>
<td>Inline</td>
<td>~60% 1,3-D + 33.3% CP</td>
<td>0.96</td>
<td>0.58</td>
<td>0.32</td>
</tr>
<tr>
<td>Telone C-35</td>
<td>49% 1,3-D + ~36% CP</td>
<td>0.44</td>
<td>0.22</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Total Amounts</strong></td>
<td></td>
<td><strong>17.66</strong></td>
<td><strong>12.86</strong></td>
<td><strong>4.13</strong></td>
</tr>
</tbody>
</table>

1) Amount of product or active ingredient
2) 56% [9.94/17.66] of all 1,3-D-containing product pounds applied were Telone II-type formulations. The remaining 43% [(6.24+0.96+0.44)/17.66] contained 33 - 60% chloropicrin.

3) Telone II comprised 75% [9.67/12.86] the 1,3-D applied in 2013.

4) Pic-Chlor 60 was the most frequently used mixture, comprising 35.5% of all 1,3-D product use per pound in 2013.

2. Physical and Chemical Properties

Because chloropicrin volatility plays a crucial role in estimating some of the occupational exposures, we have compiled physical and chemical properties information in Table 2. Both 1,3-D isomers have a lower $K_{ow}$, molecular weight and specific gravity than chloropicrin. The cis isomer has a higher Henry's Law constant and vapor pressure compared to chloropicrin. Although a wide range of soil half-lives have been reported for 1,3-D and chloropicrin, 1,3-D appears to be much more stable. Since chloropicrin is frequently used in tandem with 1,3-D, OEHHA recommends that the draft RCD should include chemical property data for chloropicrin. Consideration of environmental fate processes is essential to understanding the assumptions for many of the 1,3-D occupational exposure scenarios as they rely on chloropicrin-based data. Additional references describing the relative differences in volatility from soil and degradation in soil would be helpful.

Table 2. Physical and chemical properties of chloropicrin and 1,3-D.

<table>
<thead>
<tr>
<th></th>
<th>Chloropicrin</th>
<th>1,3-D (cis isomer)</th>
<th>1,3-D (trans isomer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Wt (g/mol)</td>
<td>164.37</td>
<td>110.98</td>
<td>110.98</td>
</tr>
<tr>
<td>Boiling point</td>
<td>112°C</td>
<td>104°C</td>
<td>112°C</td>
</tr>
<tr>
<td>$K_{ow}$</td>
<td>269</td>
<td>66.07 (2.06)</td>
<td>66.07 (2.03)</td>
</tr>
<tr>
<td>Vapor pressure @ 25°C</td>
<td>23.8 mm Hg</td>
<td>34.3 mm Hg</td>
<td>23.0 mm Hg</td>
</tr>
<tr>
<td>Henry’s Law constant atm·m$^3$/mol @ 20°C</td>
<td>2.51 x 10$^{-3}$</td>
<td>2.71 x 10$^{-3}$</td>
<td>8.71 x 10$^{-4}$</td>
</tr>
<tr>
<td>Water solubility</td>
<td>2 g/L</td>
<td>2.18 g/L</td>
<td>2.32 g/L</td>
</tr>
<tr>
<td>Specific gravity @ 25°C</td>
<td>1.656 g/ml</td>
<td>1.217 g/mL</td>
<td>1.224 g/mL</td>
</tr>
</tbody>
</table>

3. Illness Reports

Pesticide illness reporting between 1998 and 2011 found that 67 of the 72 cases related to 1,3-D exposure involved the combined chloropicrin/1,3-D mixtures. Two exposure scenarios accounted for nearly all of the reported cases: 1) bystanders (N=64, ~90%) who were exposed to chemicals from recently treated fields and 2) workers flushing tractor lines, repairing hoses or adjusting drip lines (N = 6, ~8%). In addition, two large occupational bystander incidents occurred in 2012 and 2013 but were not mentioned in the draft RCD. In both incidents, more than 40 agricultural workers were exposed after application of 1,3-D and chloropicrin formulations. It should be noted that the number of
workers affected in these two incidents exceeded the combined total reported pesticide illness cases from 2002 to 2011.

OEHHA recommends that the pesticide illness section be updated to include descriptions of the 2012-2013 incidents.

B. Pharmacokinetics

The available data on absorption, metabolism and excretion of 1,3-D are well discussed in the draft RCD. Studies in both humans and rats showed similar absorption and uptake following inhalation exposure, with absorption factors ranging from 72-82% (Waechter et al. 1992; Stott and Kastl, 1986). The major site of absorption in the rat was the lung, and to a lesser extent the nasal mucosa. Absorption of the cis- and trans-isoforms was also similar, although Stott and Kastl (1986) suggested that rats achieved higher blood levels of the trans-isoform. In humans, the major metabolites excreted were cis and trans N-acetyl-cysteine (Waechter et al. 1992). This is consistent with glutathione conjugation as the major metabolic and detoxification pathway in humans and rodents (Dietz et al. 1985).

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

The draft RCD takes into account the following exposure durations to 1,3-D by inhalation: acute, subchronic, chronic, and lifetime. No other routes of exposure were evaluated. Because the toxicity database for 1,3-D contained a sufficient number of inhalation toxicity studies spanning multiple species and durations of exposure, for non-cancer effects only inhalation studies were evaluated for dose-response analysis.

1. Acute Toxicity

In analyzing acute/short-term inhalation exposure, DPR evaluated illnesses reported in humans, as well as four acute/short-term lethal concentration LC50 studies, and body weight measurements from early time points (up to 13 days) from nine inhalation subchronic, chronic, and developmental toxicity studies conducted with experimental animals. DPR used BMD2 modeling for the acute/short-term body weight effects. The benchmark response (BMR) was set at one standard deviation (1SD) to determine the benchmark concentration at BMCL1SD. Of the five studies amenable to BMD modeling, DPR chose the BMCL1SD from male rats at 3 days in the 13 week subchronic inhalation toxicity study as the POD (49 ppm) (Stott et al. 1984).

OEHHA supports DPR’s analysis. The BMCL1SD of 49 ppm corresponds to about a 4% reduction in body weight, 6% lower than the 10% BMR generally considered for this

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2 For inhalation, the benchmark dose is an air concentration or the BMC (benchmark concentration, BMC). For risk assessment, the BMCL (95% lower confidence limit of the benchmark concentration ) is generally selected as the point of departure.
endpoint. For this 1,3-D dataset, the BMR of 1 SD is appropriate because the POD of 49 ppm is close to the estimated NOEL from two lethality ($LC_{50}$) studies (Cracknell, 1987). Rats exposed to 1,3-D at the lowest dose tested (1.62 milligram per liter, mg/L, or 357 ppm) showed partially closed eyes, breathing difficulties, hunched posture, restlessness, and pawing behavior (Cracknell, 1987). In another $LC_{50}$ study with rats, the decrease in body weight was greater than 10% at day 2 and 4 (Nitschke et al., 1990). The LOEL was reported to be 573 ppm and there was no NOEL. If a LOEL to NOEL extrapolation UF of 10-fold is applied, the estimated NOELs are 36 ppm and 57 ppm, respectively. These estimated NOELs are discussed for comparison only and are not appropriate as PODs since they are derived from a very small number of tested animals.

2. Subchronic Toxicity

DPR analyzed the rat and mouse 13-week subchronic inhalation studies by Stott et al. (1984) for subchronic toxicity exposure. Adverse effects in the rat study included reduced body weights, degeneration of the nasal olfactory epithelium, and hyperplasia of the nasal respiratory epithelium. DPR determined a NOEL of 10 ppm based on hyperplasia of the nasal respiratory epithelium. The mouse study observed similar adverse changes in body weight and nasal histopathology but also had effects on the urinary bladder and organ weight changes. The mouse NOEL was 30 ppm. Based on a lower reported NOEL, DPR chose 10 ppm for hyperplasia of the nasal respiratory epithelium from the rat subchronic study as the POD. DPR stated that BMD modeling was not used because the experimentally derived NOEL was considered “a more defensible point of departure than a putative BMCL value (page 147 in DPR, 2015).”

OEHHA agrees with using nasal epithelial effects from the rat 13-week subchronic inhalation study (Stott et al. 1984) as the critical study and adverse effect. However, OEHHA advocates the use of BMD modeling over the NOEL approach when possible. This is consistent with both US EPA and National Research Council (NRC) recommendations (NRC, 2015) on preferred dose-response analysis methodology. In the draft RCD, there is an extensive discussion supporting the use of BMD modeling (page 144 in DPR, 2015).

For mild effects from histopathology such as slight respiratory epithelial hyperplasia, we consider a BMR of 10% as sufficient. OEHHA conducted BMD modeling of histopathological lesions in the nasal turbinates at 30, 90, and 150 ppm (2/10, 10/10, and 10/10 respectively; combined very slight and slight incidences in Table III.3.b. of DPR, 2015) and yielded a BMCL10 of 10 ppm (Analysis not in this report). While the BMCL10 and NOEL are the same (10 ppm) for this dataset, the uncertainty associated with the POD derived from BMD modeling is considered lower than that from the NOEL approach. This is because the BMD modeling uses the data from the entire dose-response curve, is not constrained by the dose selection as in the NOEL approach, and incorporates the sample size and associated uncertainties into the estimate of the BMCL.
3. Chronic Toxicity

DPR analyzed two 2-year chronic inhalation studies in rats (Lomax et al. 1987) and mice (Stott et al. 1987). The only non-cancer adverse effects noted in rats were effects on body weight and on nasal olfactory histopathology, mostly limited to the highest dose tested (60 ppm) (Table III.6.b. in DPR, 2015). The NOEL was 5 ppm based on nasal histopathology. In the mouse study, the NOEL was also 5 ppm but more histopathological changes were reported at the LOEL of 20 ppm, including: urinary bladder mucosal hyperplasia in females, nasal respiratory epithelial hyperplasia in females. Hyperplasia of the non-glandular stomach in males was also reported at 60 ppm (Table III.7.b. in DPR, 2015). Thus, the mouse was determined to be the most sensitive species because of the more severe effect at the LOEL and lower HEC (0.16 ppm) compared to that (0.20 ppm) for the rat (Table IV.2.a, page 98 in DPR, 2015). Thus, the NOEL of 5 ppm from the chronic mouse study was cited as the POD. DPR apparently conducted BMD modeling but decided to "retained the experimentally determined NOEL (page 147 in DPR, 2015)" because the BMCL (unadjusted dose of 5 ppm) was the same as that reported by the US EPA.

OEHHA agrees with the selection of the chronic mouse study (Stott et al. 1987) as the critical study. However, OEHHA recommends BMD modeling of appropriate endpoints when possible.

D. Developmental and Reproductive Toxicity

OEHHA agrees with the conclusion in the draft RCD that there are appropriate reproductive and developmental toxicity studies to meet registration requirements (Breslin et al. 1989; John et al. 1983). Breslin et al. (1989) found no evidence of reproductive toxicity in a two-generation inhalation reproduction study in Fischer 344 rats. There was no significant toxicological effect on mating or fertility, or effects on pup weight or survival. John et al. (1983) also found no evidence of developmental toxicity in developmental toxicity inhalation studies conducted in two species (Fischer F344 rats and New Zealand white rabbits), even at doses that were clearly maternally toxic.

E. Carcinogenicity Weight of Evidence

1. Genotoxicity

In the draft RCD, there is an extensive discussion of in vivo and in vitro genotoxicity studies of 1,3-D (Table III.11a in DPR, 2015). OEHHA agrees with the conclusion that 1,3-D is genotoxic due to multiple positive in vivo and in vitro studies in the genotoxicity database. While there are negative studies and some questions regarding positive results in the presence of confounding impurities, epichlorohydrin as a stabilizer, and oxidation products (Stott et al. 2001; Eder et al. 2006; Klaunig et al. 2015), it is OEHHA’s opinion that they are not sufficient to discount the positive genotoxicity data.
2. Human and Experimental Animal Evidence of Carcinogenicity

In the draft RCD, DPR found 1,3-D was oncogenic in several animal studies including those by inhalation, dietary, and gavage exposure (summarized in Table 3). While the lung tumor from inhalation exposure was considered most relevant, the two-year dietary study in rats (Stott et al. 1995) was discussed as part of the weight of evidence evaluation. There was a statistically significant increase in liver adenoma and carcinoma at the highest dose tested. This tumor type was considered to be related to the exposure route since it was not found in inhalation toxicity studies. The results from the NTP gavage studies with rats and mice (NTP, 1985) were briefly described in the Risk Appraisal section (page 148 in DPR, 2015) as support for the determination of 1,3-D oncogenicity. These studies found forestomach squamous cell papillomas and squamous cell carcinomas and hepatic neoplastic nodules in rats and urinary bladder transitional cell carcinomas, lung tumors (bronchioalveolar adenoma and carcinoma), and forestomach tumors in mice.

A couple of studies in humans implicated exposure to 1,3-D with increased cancer risk: fatal histocytic lymphoma in two emergency responders six years after exposure to 1,3-D from a tank truck spill, and the association between 1,3-D use and death from pancreatic cancer in three counties (page 148 in DPR, 2015).

Table 3: Tumor findings in experimental animals (DPR, 2015).

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>Tumor found (Data in draft RCD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Inhalation</td>
<td>None</td>
<td>Lomax et al. 1987</td>
</tr>
<tr>
<td>Mouse</td>
<td>Inhalation</td>
<td>Bronchioalveolar adenoma (Table III.7.c.)</td>
<td>Stott et al. 1987</td>
</tr>
<tr>
<td>Rat</td>
<td>Dietary</td>
<td>Liver adenoma and carcinoma (Table III.8.)</td>
<td>Stott et al. 1995³</td>
</tr>
<tr>
<td>Rat</td>
<td>Gavage</td>
<td>Forestomach squamous cell papillomas and squamous cell carcinomas, and hepatic neoplastic nodules</td>
<td>NTP, 1985</td>
</tr>
<tr>
<td>Mouse</td>
<td>Gavage</td>
<td>urinary bladder transitional cell carcinomas, lung tumors (bronchioalveolar adenoma and carcinoma), and forestomach tumors</td>
<td>NTP, 1985</td>
</tr>
</tbody>
</table>

OEHHA agrees with DPR’s conclusion that 1,3-D is an animal carcinogen based on increased tumor incidence found in both rats and mice following both oral and inhalation exposures and positive genotoxicity data. US EPA and IARC classified 1,3-D as a probable human carcinogen (US EPA, 2000; IARC, 1987). 1,3-D is listed under

³ This study was published as Stebbins et al. 2000.
Proposition 65 as a carcinogen. OEHHA recommends that the two NTP studies should be included in the Toxicology Profile for a comprehensive presentation of the database.

3. Mechanism for Carcinogenicity

DPR provided a thorough weight of the evidence evaluation and concluded that the carcinogenicity of 1,3-D is mediated via a genotoxic MOA. Following US EPA’s cancer risk assessment for 1,3-D (US EPA, 2000), Dow Chemical Company had published its own risk assessment and toxicity review with the position that 1,3-D carcinogenicity is via a non-genotoxic mode of action (MOA) and the chemical should be treated as a threshold carcinogen (Driver et al. 2014; Stott et al. 2001). The proposed MOA involved glutathione depletion in target tissues where tumors were formed, although they also asserted that the evidence for carcinogenicity in the lung is weak (Driver et al. 2014). Klaunig et al. (2014) also proposed a similar non-genotoxic MOA for the hepatocellular adenoma tumors found in a two-year dietary study in Fischer rats (Stott et al. 1995).

OEHHA concurs with DPR that the genotoxicity evidence supports a non-threshold mechanism for the carcinogenicity of 1,3-D.

4. Cancer Potency Determination Approach

The draft RCD used the tumor incidences from the Stott et al. (1987) study for bronchioalveolar adenomas in male mice with a positive dose-response relationship to calculate cancer potency. The incidence rate was statistically significant at the highest dose tested (Table III.7.c., page 56 in DPR, 2015). To determine the denominator for tumor incidence, DPR assumed the number of animals at risk was the number of animals still alive at 52 weeks of the study. Tumors were modeled using the linearized multistage cancer model with a benchmark response of 10% extra risk to determine the potency.

In the draft RCD, cancer potency was calculated assuming the lung tumors were due to direct contact of 1,3-D at the trachea-bronchial and pulmonary regions and thus a portal of entry RGDR was applied for interspecies scaling. The calculated human equivalent potencies for residents/bystanders and workers were 0.018 ppm$^{-1}$ and 0.0059 ppm$^{-1}$, respectively (Table IV.3., page 102 in DPR, 2015).

OEHHA has several recommendations regarding the calculation of the potency of 1,3-D. When calculating animals at risk, OEHHA suggests using animals alive at the appearance of the first tumor, rather than choosing animals alive after one year. While this only results in one fewer animal being counted in the 5 ppm dose group in the Stott et al. study (see Table 4 below), it is a more appropriate representation of animals at risk and is consistent with DPR’s approach used in the chloropicrin RCD (DPR, 2012).

OEHHA disagrees with the use of the RGDR methodology for interspecies extrapolation when calculating cancer potency. As already discussed, the lung tumors should be
considered a systemic effect. OEHHA recommends the use of body weight scaling to the $\frac{3}{4}$ power, when calculating human equivalent cancer potency (Table 4). The potencies are approximately 24-fold higher than those derived from the RGDR approach (0.018 ppm$^{-1}$ and 0.0059 ppm$^{-1}$). When expressed in units of mg/kg-day term, the OEHHA-calculated potencies are 0.05 and 0.017 milligram per kilogram-day (mg/kg-day)$^{-1}$ for non-workers and workers, respectively. The residential potency is of similar magnitude as that (0.055 mg/kg-day$^{-1}$) calculated in the DPR 1997 risk assessment (DPR, 1997). The slightly higher DPR potency is due to a higher body weight scaling factor (0.695) using a lower mouse body weight of 0.03 kilogram (kg).

Table 4: Time adjusted dose and cancer potencies for bronchioalveolar adenomas in male mice from Stott et al. 1987.

<table>
<thead>
<tr>
<th>Nominal Dose (ppm)</th>
<th>Time adjusted dose (ppm)$^5$</th>
<th>Tumor incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-workers$^b$</td>
<td>Workers</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.82</td>
<td>2.46</td>
</tr>
<tr>
<td>20</td>
<td>3.29</td>
<td>9.86</td>
</tr>
<tr>
<td>60</td>
<td>9.86</td>
<td>29.57</td>
</tr>
<tr>
<td>Animal potency (ppm$^{-1}$)</td>
<td>0.062</td>
<td>0.021</td>
</tr>
<tr>
<td>Animal potency (mg/kg-day$^{-1}$)</td>
<td>0.0076</td>
<td>0.0026</td>
</tr>
<tr>
<td>Body weight scaling factor$^b$</td>
<td>6.6</td>
<td>6.6</td>
</tr>
<tr>
<td><strong>Human potency (mg/kg-day$^{-1}$)</strong></td>
<td><strong>0.050</strong></td>
<td><strong>0.017</strong></td>
</tr>
</tbody>
</table>

$^{**}$p<0.01 Significance by Trend test (indicated at the control group) and Fisher Exact test.

$^a$Used DPR default breathing rate for mouse 1.8 m$^3$/kg-day and 4.54 mg/m$^3$ per ppm factor

$^b$Body weight scaling factor: (human body weight/mouse body weight)$^{0.25}$= (70 kg/0.0373 kg)$^{0.25}$=6.6

$^b$Non-occupational bystanders and residential bystanders

As shown in Table 3, 1,3-D also caused cancer through oral routes. OEHHA recommends a more comprehensive evaluation of tumor findings across all exposure routes, to ensure the highest potency is used to estimate human cancer risk. Further, multisite tumor analysis should be conducted for the two NTP studies (1985) where more than one tumor type was found in the test animals.

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$^4$The amount of chemical per body weight scaled to the three-quarters power is assumed to result in the same degree of effect across species. Scaling to the estimated human potency (Potency$_{human}$) can be achieved by multiplying the animal potency (Potency$_{animal}$) by the ratio of human to animal body weights (BW$_h$/BW$_a$) raised to the one-fourth power.

$^5$Dose (ppm) from animal studies is adjusted for purity and human exposure duration. Non-occupational bystander and residential bystander:

Worker:

Time adjusted dose = (nominal dose) x (92% purity) x (6 hr / 8 hr) x (5 days / 7 days)
5. Co-Exposure to Chloropicrin

The potential of an enhanced respiratory toxicity from co-exposure to chloropicrin, which is included in many of the 1,3-D formulations, was not addressed in the draft RCD. This is important to note because DPR’s final RCD for chloropicrin reported slight increase in lung adenomas in female CD-1 mice exposed to chloropicrin for 78-weeks, the duration of the inhalation toxicity study. This increase was statistically significant in trend (p<0.05) and approached significance (p>0.053) for Fisher’s exact test.

F. Extrapolation, Variability, and Uncertainty

1. Interspecies Extrapolation and RGDR Approach

To convert inhalation doses from animal studies to Human Equivalent Concentrations, OEHHA supports DPR’s use of the RGDR methodology developed by US EPA for non-cancer adverse effects (US EPA, 1994). When the adverse effect is the result of systemic metabolism and distribution, the assumption is that the difference in breathing rates and surface areas between humans and the animal model is not important, because the distribution of the chemical between the blood and the air in the lung reaches equilibrium. Thus, the default RGDR is a value of 1, based on the same blood:air partition coefficients for humans and animals. When the adverse effects are in the respiratory tract and considered portal of entry effects, it is assumed that the locally absorbed dose is the critical dose metric and is a function of breathing rates and surface area at the site of deposition and absorption. In the draft RCD, DPR assumed a systemic effect for short-term effects on body weight and portal of entry effects for subchronic and chronic nasal respiratory effects. OEHHA agrees with DPR’s assumptions yet has some comments on the values used in the calculations for subchronic and chronic toxicity.

Subchronic: DPR assumed a portal of entry approach for nasal epithelial effects and calculated the RGDR value as 0.115. OEHHA agrees with the RGDR value and again, advocates use of the BMCL as the POD.

Chronic: DPR based their NOEL on both portal of entry (nasal respiratory epithelial changes) and systemic (urinary bladder epithelial changes) effects in the two-year inhalation mouse study. DPR applied the RGDR value for portal of entry, extrathoracic effects of 0.198 over the assumed systemic RGDR value of 1 as a more health protective approach. OEHHA agrees with this rationale and the use of the lower RGDR

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6 The equation for HEC is:
HEC = POD x (formulation purity) x (Da / Dh) x (Wa / Wh) x RGDR, with a=animal, D=days, h=human, and W=weeks.
value. However, OEHHA recommends use of the BMCL_{10} for nasal epithelial hyperplasia as the chronic POD.

2. Uncertainty Factors

For the RGDR approach for non-cancer effects, DPR decreased the conventional interspecies UF of 10 to $\sqrt{10}$. This is based on the assumption that the RGDR already accounted for the pharmacokinetic portion of the interspecies factor. OEHHA agrees that if a chemical is causing a portal of entry effect and local metabolism is generally not a concern, the reduction in the pharmacokinetic portion of the UF to a value of 1 is appropriate. However, when the critical effect is systemic in nature, and may involve metabolism, a UF for interspecies pharmacokinetics should be retained with a value of 2 to account for potential uncertainty (OEHHA, 2008). Thus, this interspecies UF of 2 should be considered for the reduced body weight from acute exposure to 1,3-D. The total interspecies UF would then be 6, not 3 (rounded).

In the draft RCD, the intraspecies UF is 10-fold, with $\sqrt{10}$ for pharmacokinetic and $\sqrt{10}$ for pharmacodynamic differences in the human population. As discussed under “Sensitive Population,” OEHHA suggests an increase of the intraspecies pharmacokinetic UF to a value of 10, for a total intraspecies UF of 30 ($10 \times \sqrt{10}$, rounded).

3. Sensitive Population

In the draft RCD, DPR applied an additional UF of 3 and calculated separate margins of exposures (MOEs) to address concerns over potentially enhanced susceptibility of infants and children to the non-cancer effects of 1,3-D. The basis for this concern is a data gap: there are no data on the surface areas of different lung regions for young animals and small children that allow the RGDR approach for interspecies dose extrapolation.

For non-cancer effects, OEHHA’s view is that there are many factors affecting human variability in response to a chemical (OEHHA, 2001, 2008; Zeise et al. 2013). Thus, OEHHA’s practice is to increase the traditional intraspecies pharmacokinetic UF of $\sqrt{10}$ to 10 (OEHHA, 2008). This increase would account for subpopulations such as children, pregnant women, and the elderly, possibly being more sensitive than the general population to the toxicity of a chemical and reflects the wide variability in pharmacokinetics across age groups. Thus, OEHHA recommends DPR expand their concerns for children and increase the intraspecies pharmacokinetic UF to 10. This would apply to sensitive individuals in worker, bystander, and resident populations.

OEHHA is also concerned about increased sensitivity to carcinogens due to early life exposure. OEHHA calculates and applies adjustments, or age sensitivity factors (ASFs), to different age groups, for all carcinogens (OEHHA, 2009). The default ASFs are 10 for fetuses in the third trimester to children <2 years old, 3 for children 2 years to
<16 years old, and 1 for adults age 16 to 70 years old. The lifetime risk is then the sum of the cancer risks for each life stage, which is calculated as age-appropriate exposure x cancer potency x ASF. An example of the calculations for residential exposure using the ASF and the 95th percentile point estimates of daily breathing rate (BR) is shown in Table 5. The 95th percentile BR is recommended to represent people doing all types of activities. The inclusion of these factors increased the cancer risk by about three-fold.

Table 5. Cancer risk with age-sensitivity factor and breathing rate applied.

<table>
<thead>
<tr>
<th>Life Stages</th>
<th>BR a m³/kg-day</th>
<th>FD</th>
<th>ASF adjustment</th>
<th>No ASF adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASF a</td>
<td>BR and ASF adjusted exposure</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>0.361</td>
<td>0.25/70 10</td>
<td>2.3x10⁻⁵</td>
<td>1.1x10⁻⁶</td>
</tr>
<tr>
<td>Infant</td>
<td>1.09</td>
<td>2/70 10</td>
<td>5.5x10⁻⁴</td>
<td>2.7x10⁻⁵</td>
</tr>
<tr>
<td>Child</td>
<td>0.745</td>
<td>14/70 3</td>
<td>7.9x10⁻⁴</td>
<td>3.9x10⁻⁵</td>
</tr>
<tr>
<td>Adult</td>
<td>0.29</td>
<td>54/70 1</td>
<td>3.9x10⁻⁴</td>
<td>2.0x10⁻⁵</td>
</tr>
<tr>
<td>Total lifetime risk</td>
<td></td>
<td></td>
<td>8.8x10⁻⁵</td>
<td></td>
</tr>
</tbody>
</table>

a The 95th percentile breathing rates from Tables 3.1 (OEHHA, 2012).

b Exposure= ppm air concentration x BR x FD x ASF

Air concentration=0.3878 ppb (0.00176 mg/m³) for male, birth to age 70, from HEE5CB modeling (Table IV.8, page 133 of DPR, 2015). Inhalation absorption assumed at 100%

c Risk= adjusted exposure x potency (0.050 mg/kg-day⁻¹ from Table 4 for non-workers of this report).

Abbreviations: ASF=age-sensitivity factor, BR=breathing rate, FD=fractional duration in a 70 year lifetime

G. Exposure Assessment

The exposure assessment for 1,3-D is complex using multiple data sources and assumptions, and calculation methodologies. A flow chart or summary table to illustrate key information would be helpful. For this review, OEHHA has constructed three tables (Tables 6, 7, and 8) to show areas of concern (shown as bolded text in the Tables).

1. Handler Exposure Estimates

Handlers include fumigant applicators, fumigant loaders and tarp removers (Table 6).

The short- and long-term breathing-zone air concentrations and occupational exposure estimates were generated using four different sources of data and information. These sources included:
1,3-D breathing-zone air concentration data generated by the registrant (Houtman, 1993)
- chloropicrin air monitoring data, used as a surrogate for 1,3-D (DPR, 2010)
- simulated air concentrations (DPR, 2009a)
- a 14-month 1,3-D ambient air monitoring study conducted by the registrant (Rotondaro and van Wesenbeeck, 2012a)

Air concentrations for the shank application with tarp, drip application, hand-wand application and tarp remover scenarios were generated using ratios based on chloropicrin field studies.

Table 6. Summary of occupational exposure estimation parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Handler</th>
<th>Reentry worker</th>
<th>Occupational bystander</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Applicators</td>
<td>Loader</td>
<td>Tarp remover</td>
</tr>
<tr>
<td>Location</td>
<td>At treated field</td>
<td>At treated field</td>
<td>At treated field after REI of 7 days</td>
</tr>
<tr>
<td>Air concentration data source</td>
<td>1,3-D breathing zone data and chloropicrin data</td>
<td>1,3-D breathing zone data</td>
<td>1,3-D breathing zone data and chloropicrin data</td>
</tr>
<tr>
<td>STAC</td>
<td>8 hr TWA 1,3-D data 95th %-tile of log measured breathing zone concentration, adjusted for recovery, application rate, APF Chloropicrin data Adjust chloropicrin data with 1,3-D ratios</td>
<td>8 hr TWA 1,3-D data Only one of the 3 application conditions was estimated, adjusted for application rate, APF</td>
<td>8 hr TWA 1,3-D data 95th %-tile of log measured breathing zone concentration, adjusted for recovery, application rate, no APF Chloropicrin data Adjust chloropicrin data with 1,3-D ratios</td>
</tr>
<tr>
<td>SAC</td>
<td>Daily 8 hr over 8 months Mean air concentration from 3 study sites Seasonal application rate</td>
<td>Daily 8 hr over 8 months Mean of 5 values</td>
<td>Measured air concentrations from Merced data</td>
</tr>
<tr>
<td>AAC</td>
<td>SAC amortized over 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>AAC amortized 40 years/70 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AAC=annual air concentration, APF=assigned protection factor, hr=hour, ISCST3=Industrial Source Complex Short-term version 3, LAC=lifetime air concentration, REI= restricted entry interval, SAC=seasonal air concentration, STAC=short-term air concentration, TWA=time-weighted average.
a) **Applicator (shallow shank without tarp)**

The exposure estimate made for the shallow shank without tarp scenario is a key value. It was the only applicator value based on actual 1,3-D field measurements and was also used as a reference value for computing estimates for other scenarios based on chloropicrin field data. Breathing zone concentrations of both 1,3-D and chloropicrin were measured directly for five applicators/drivers during approximately 4 hours of exposure. The 95th percentile of a lognormal distribution of exposure concentrations was calculated as described (DPR, 2009b) and used as the short-term air concentration estimate (STAC) of 2347 μg/m³ (0.52 ppm).

The spillage control assumption was not explained in sufficient detail to critique and the rationale for excluding the applicator “high exposure potential activities” from the draft RCD exposure estimates was not clear despite a discussion in the exposure appraisal.

The original data set had 5 samples and spanned a ~100-fold range. DPR removed the lowest value and the remaining 4 samples covered only a 10-fold range. However, no formal outlier analysis process was described. OEHHA conducted an outlier analysis (Grubbs’ Test, GraphPad Software, 2015) which revealed no significant outlier for either the original exposure data or log-transformed values (0.05 significance level, n=5, two-sided analysis). The supporting reference notes that it is not uncommon to have air concentrations spanning a range of more than 10-fold (DPR, 2009b).

Also, the calculation of the 95th percentile of the lognormal distribution of exposure concentrations used the “population” standard deviation formula, which would be appropriate for very large populations but is known to frequently underestimate the standard deviation. Because the four exposure values cited in the draft RCD are used to estimate exposure for a much larger population of handlers exposed to 1,3-D under specific conditions (shallow shank, no tarp), the sample standard deviation is more appropriate (Minium and Clarke, 1982).

b) **Chloropicrin-based Exposure Estimates for Four Applicator Scenarios and the Tarp Remover Scenario**

The exposure estimates for these five scenarios all employed ratios derived from chloropicrin field data. Using the values from a common application scenario (shallow shank, no tarp) and assuming a directly proportional relationship, five ratios were used to estimate 1,3-D air concentrations. The rationale and underlying assumptions for these calculations were not provided in the RCD.
Using the above assumptions, the following relationship was derived:

\[
\frac{[\text{chloropicrin}]_{\text{SS, with tarp}}}{[\text{chloropicrin}]_{\text{SS, no tarp}}} = \alpha \frac{[1,3-\text{D}]_{\text{SS, with tarp}}}{[1,3-\text{D}]_{\text{SS, no tarp}}}
\]

SS = shallow shank
By re-arranging equation 3, then we have

\[
[1,3-\text{D}]_{\text{SS, with tarp}} = \alpha [1,3-\text{D}]_{\text{SS, no tarp}} \times \left(\frac{[\text{chloropicrin}]_{\text{SS, with tarp}}}{[\text{chloropicrin}]_{\text{SS, no tarp}}}\right)
\]

\[
[1,3-\text{D}]_{\text{SS, with tarp}} = 2347 \, \mu g/m^3 \times (1880/637) = 6926 \, \mu g/m^3 = 1.53 \, \text{ppm}
\]

The same surrogate chemical assumption was subsequently applied to both drip applicators, hand-wand applicator and tarp remover estimates.

We are concerned that the method used to predict 1,3-D exposure for tarp removers could underestimate exposure by an order of magnitude or more. Tarp removal occurs several days after 1,3-D application and does not require personal protective equipment. As in the other scenarios, chloropicrin and 1,3-D were assumed to behave similarly in the soil. However, chloropicrin dissipates relatively quickly under tarped conditions so that relatively little (0.2-5% of total applied) is emitted after tarp cutting at the sixth day. Under the same conditions, the 1,3-D flux rate surged in the twenty-four hours after tarp cutting and accounted for 23-53% of the total applied (Qin et al. 2011).

Also, these exposure estimates have three sources of variability: the 1,3-D estimate (for shallow shank, no tarp) and the two chloropicrin estimates used to derive the application-method-specific ratio. The draft RCD only considered one source of variability and the other two were not addressed.

Lastly, the condensed descriptions of these occupational exposure estimate calculations were somewhat difficult to follow and reproduce. If the specific calculations and assumptions were presented in a separate appendix, it would greatly increase the transparency of the underlying calculations.

\( c)\) Loader

Short-term exposure estimates for loaders were calculated directly from breathing-zone measurements of 1,3-D under field conditions (Houtman, 1993). The draft RCD excluded “high exposure potential activities” from the loader exposure scenario. No clear justification was provided. DPR should provide a rationale for not taking the same approach that was used by US EPA in estimating exposures for this activity.

\( d)\) Reentry Worker
The restricted entry interval (REI) for 1,3-D is supposed to be 7 days, but the draft RCD (page 116) describes several post-fumigation activities shorter than 7 days, including bed shaping (3-24 hours post-fumigation), rock removal (2.7 days post-fumigation) and center pivot maintenance and winterization (3.8 days post-fumigation). Since the exposure concentration for reentry workers was calculated using data from an air monitoring study conducted 3.8 days post-fumigation, exposures for some reentry activities (bed shaping and rock removal) could be underestimated. OEHHA recommends that DPR (1) clarify why some activities can take place before the end of the REI and (2) estimate the uncertainty in using a study conducted 3.8 days post-fumigation as representative of all reentry activities.

**e) Maintenance Worker**

In order to prevent 1,3-D-related corrosion, workers routinely flush this chemical from application equipment, tractor supply lines, repair hoses or adjust drip lines. Furthermore, illness reports indicate maintenance activities occasionally result in illness cases (~8% of the 1,3-D-related pesticide illness reports). The draft RCD should include equipment cleaning and maintenance in its occupational exposure assessment.

### 2. Occupational Bystander Exposure Estimates

The occupational bystander could be a worker in a field adjacent to the field undergoing fumigation (Table 6). No buffer zone or personal protective equipment was incorporated into the exposure assessment.

**a) Short-term exposure estimates**

The 8-hour time-weighted average (TWA) concentrations (STAC) were calculated from measured flux rate data extracted from various 1,3-D field studies for different application methods (DPR, 2009a). The method and assumptions used to calculate short-term exposure estimates appear to be reasonable.

**b) Longer-term (seasonal, annual and lifetime) exposure estimates**

Measured concentrations from the 14-month continuous air monitoring study in Merced County were used for longer-term occupational bystander exposure estimates of seasonal air concentration (SAC), annual air concentration (AAC), and lifetime air concentration (LAC) (Rotondaro and van Wesenbeeck, 2012b). These data were assumed to be representative of ambient 1,3-D air concentrations in other high-use regions.

OEHHA concurs with the methods and assumptions used to calculate the longer term occupational bystander exposure estimates as being health-protective. However, we
found that the method and rationale for applying the eight-month Fresno County use season to the Merced County data is not clearly explained.

3. Residential Bystander Exposure Estimates (Edge of Buffer Zone)

Both short- and long-term 1,3-D breathing-zone air concentrations for a residential bystander located 100 feet from the edge of the treated field were estimated from simulated air concentrations by well-established methods (DPR, 2000a; DPR, 2009a; DPR, 2009c) (Table 7). OEHHA agrees with DPR’s identification of the field data that provided a basis for these exposure concentrations and the methods that were used to estimate them.

The exposure appraisal notes that peak 24-hour air concentrations in high-use areas could have exceeded the recorded values due to monitoring study limitations (limited number of sampling stations, choice of sampling rates and sample intervals) as well as untimely equipment failure or vandalism. For example, the Merced study used one sampling station per 36 square mile township.

Table 7. Summary of non-occupational exposure estimation parameters.

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Residents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Residential bystander</td>
</tr>
<tr>
<td></td>
<td>Edge of <strong>buffer zone</strong> (100 feet)</td>
</tr>
<tr>
<td>Fumigation type</td>
<td>Shank and drip</td>
</tr>
<tr>
<td>Air concentration Data</td>
<td>1,3-D air monitoring data</td>
</tr>
<tr>
<td>STAC 24-hr TWA</td>
<td>1,3-D estimated data</td>
</tr>
<tr>
<td>ISOCT3 modeling, maximum flux rate, adjusted application rate, 100 feet buffer zone.</td>
<td>1,3-D estimated data</td>
</tr>
<tr>
<td>SAC Daily 24 hr over 14 days</td>
<td>Not calculated due to lack of long-term model</td>
</tr>
<tr>
<td>1,3-D simulated data Two-week flux modeling Mean application rate</td>
<td>Not calculated due to lack of long-term model</td>
</tr>
<tr>
<td>AAC SAC amortized over 12 months</td>
<td>Highest one-year mean at Township 5 from the Merced data</td>
</tr>
<tr>
<td>Mean application rate</td>
<td>Not calculated due to lack of long-term model</td>
</tr>
<tr>
<td>LAC</td>
<td>Same as AAC</td>
</tr>
</tbody>
</table>

AAC=annual air concentration, HEE5CB=High-End Exposure version 5, Crystal Ball, hr=hour, LAC=lifetime air concentration, MCABLE=Monte Carlo Annual-Based Lifetime Exposure model, SAC=seasonal air concentration, SOFEA=Soil Fumigant Exposure Assessment System, STAC=short-term air concentration, TWA=time-weighted average.

The draft RCD notes a concern regarding overestimation of short-term exposure “based on the presumption that a resident will spend 24 continuous hours either at 100 feet from a treated field, or in an area with elevated ambient air concentration of 1,3-D, or both.” Although this assumption may appear to be conservative, it seems reasonable because of the close proximity of agricultural fields to homes, schools and workplaces within the high-use areas.

a) Residential bystanders (shank & drip applications)

STAC levels were based in part on the assumption that there is only one application per year. Is there any evidence which suggests that more than one application per year occurs for some formulations or crops?

Another assumption is that virtually all 1,3-D volatilizes within 14 days of application. Although testing under laboratory conditions showed that emissions plateau within 2 weeks, field studies did not seem to fully validate this observation (Kim et al, 2003; Gao et al. 2009). This data suggests that cumulative impacts from applications to more than one field in the neighborhood of one residential area may be significant for some residents, particularly in high 1,3-D use areas.

b) Residential bystander buffer zones

OEHHA has concerns about how buffer zones are modeled in calculating residential bystander exposure estimates. It is our understanding that the 100-foot buffer zone only applies to “occupied structures.” Does this mean a resident working in his/her backyard can be less than 100 feet from the application site of 1,3-D? This issue requires clarification.
c) **Cumulative exposure of residents to ambient and non-ambient sources**

OEHHA agrees that summation of both nearby and ambient sources exposure, as suggested in the draft RCD, is both reasonable and health-protective.

d) **Residential bystanders ambient exposure: STAC, SAC and AAC**

In the 2012 Merced County study, air samples were continuously collected every 72 hours in nine adjacent townships from October 2010 to January 2012 (Rotondaro and van Wesenbeeck, 2012b). The highest one-day 1,3-D concentration recorded during this study was 369.2 μg/m³, which was used as the residential bystander ambient air STAC. Both the SAC and AAC for residential ambient exposure were also obtained from the same Merced study. The mean SAC (11 μg/m³) occurred in the same high use township during the January-April 2011 and September-December 2011 high use periods. The AAC value (7.91 μg/m³) was also recorded at the same site. OEHHA concurs with DPR’s methodology for estimating short-term, seasonal and annual exposure concentrations using the data from the Merced County study.

e) **Residential bystanders ambient exposure: Lifetime air concentrations (LAC)**

Because there are no long-term monitoring studies applicable to residential lifetime ambient exposure estimates, simulated air concentrations coupled with stochastic (i.e., probabilistic) human exposure assessment models were used.

The SOil Fumigant Exposure Assessment System (SOFEA©) (Cryer et al. 2005) was developed by Dow AgroSciences specifically to calculate 1,3-D residential exposure. SOFEA uses the ISCST3 dispersion modelling software to simulate air concentrations and incorporates additional factors to account for crop type, application method and use patterns (DPR, 2005).

OEHHA has the following comments on the use of ISCST3 and SOFEA-based exposure estimates:

- The 2007 US EPA Human Health Risk Assessment for 1,3-D states that ISCST3 does not quantitatively address calm conditions and “a process has been used where calm conditions (i.e., wind speeds less than 1 meter per second) are dropped from calculations and a time-weighted average result is calculated without those values. This approach is consistent with how ISCST3 has been historically used” (US EPA, 2007). We assume that this same filtering process is applied by the ISCST3-based calculations in SOFEA. Since this filtering process could lead to under-estimating the average 1,3-D air concentrations, would it be
possible to estimate the frequency that these “calm conditions” occur in high-use areas during high-use months? This information could serve as both a potential indicator for the frequency of high risk conditions as well as an index of how often the data have been altered by this filtering effect.

- The Central Valley has historically experienced prolonged periods of overcast weather and fog during the winter months. These conditions coincide with low temperature conditions (0-7°C) and could alter dissipation of 1,3-D. Are these not-uncommon regional conditions accounted for within the weather data inputs for SOFEA?

- Following technical discussions with DPR staff, we have increased confidence that the SOFEA-2 air dispersion model has been suitably modified so that many of the concerns raised in the 2004 US EPA review have been addressed (US EPA, 2004). The most recent SOFEA-2 modifications (mixing height, atmospheric stability class designation, border township effects) are part of a continued effort to address dispersion model limitations (periods of low or no wind speed). However, the fact that the 1,3-D emissions from more distant townships can and do influence the accuracy of predicted air concentrations within the inner 9 high-use townships (van Wesenbeeck et al. 2015) further underscores the complexity of the modelling process.

- The exposure estimates predicted by HEE5CB were higher than the MCABLE-based estimates. As stated on page 163, “To minimize the impact of infrequent occurrence of high 1,3-D air concentrations in SOFEA-2 predictions, for the HEE5CB simulations, the ranges of input air concentrations were restricted to those that bracketed the mean observed value in Township #5”. Because the Township #5 concentrations were the highest in the entire nine township area, selecting a subset of the simulated annual values which clustered around those peak values would bias the final estimate towards the highest concentrations. In contrast, the MCABLE estimates were based on all one hundred years of simulated annual average air concentrations, thus the MCABLE analysis would reflect all possible simulated values from all nine townships (36 square mile/township x 36 receptors/square mile x 9 townships = 11,664 receptors over the entire area x 100 years). Since many of those simulated values would come from receptors with much lower 1,3-D levels, this approach generates a more “diluted” value as the influence of the Township #5 values is diminished by a larger denominator.

OEHHA concurs with DPR’s use of a modified air concentration data set in combination with the HEE5CB model to provide a conservative estimate of residential ambient lifetime exposure.
f) Residential Mobility

Two different models were used to account for the effects of mobility on lifetime exposure (Table 8).

Table 8. Comparison between MCABLE and HEE5CB models.

<table>
<thead>
<tr>
<th>Developer</th>
<th>MCABLE</th>
<th>HEE5CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenarios</td>
<td>Dow Chemical Company</td>
<td>DPR</td>
</tr>
<tr>
<td>Considered</td>
<td>Considers the relative amount of time that an individual (age 18 or older) spends in a highest-exposure township and its surrounding townships within a high 1,3-D use area. Also, the age of an individual who moved in and out of the area;</td>
<td>Low mobility - exposures are simulated based solely on the distribution of 1,3-D air concentrations from the highest-exposure township, township #5 (at the center of the 3x3 township grid). This setting is equivalent to stating that individuals spend their entire lives (i.e., from birth to age 70) in township #5.</td>
</tr>
<tr>
<td></td>
<td>• the fraction of time that an individual is temporarily outside the high use area;</td>
<td>Intermediate mobility - air concentration distributions of 1,3-D from both the highest-exposure township (township #5) and the surrounding eight townships. Under this intermediate mobility assumption, individuals are allowed to spend time (i.e., “move around”) within five of the nine different townships; however, township #5 is considered “home” (i.e., an individual spends most of his/her time there) and other four are considered “away from home.”</td>
</tr>
<tr>
<td></td>
<td>• The number of years that an individual resides in a single residence within the highest-exposure township before moving into other townships (up to three times) within the same area</td>
<td>High mobility – both the “home” and “away from home” townships could be any of the nine townships.</td>
</tr>
<tr>
<td>Age</td>
<td>Considered</td>
<td>Allows for time spent at the “home” township to change with age: decreases from 80% for infants to 60% for adults</td>
</tr>
<tr>
<td>Mobility Survey</td>
<td>Kaplan, 2014</td>
<td>Wiley, 1991 a and b</td>
</tr>
</tbody>
</table>

HEE5CB=High-End Exposure version 5, Crystal Ball, MCABLE=Monte Carlo Annual-Based Lifetime Exposure model.
1. HEE5CB (DPR, 1997) has three different mobility scenarios, as described in Table 8. The model varies the amount of time an individual spends in a 3x3 township grid, with the center township (#5) having the highest concentration. Time spent in different townships changes with an individual’s age. Actual time allocation among these townships is treated in HEE5CB as a stochastic multinomial variable. The proportion of time an individual spends in each location was derived from two surveys concerning daily activity patterns of California residents and was treated in the model as a stochastic multinomial variable (Wiley, 1991 a and b).

2. MCABLE considers the relative amount of time that an individual (age 18 or older) spends in a highest-exposure township and its surrounding townships within a high 1,3-D use area (see Table 7). Like HEE5CB, MCABLE incorporates assumptions regarding the mobility of an individual within and outside the exposure area, a 3x3 township grid. Certain variables in MCABLE were selected randomly from three separate custom distributions developed by Driver (2015) based on a California-specific residential mobility survey (Kaplan, 2014). The survey was given in both English and Spanish with only one participant per household. The Merced survey area included four townships where demand for 1,3-D regularly exceeded the 90,250 pounds township cap.

OEHHA has the following concerns and comments on the resident mobility models:

1. The exposure estimates for the HEE5CB model were based on two telephone survey studies and physiological population metrics that may be somewhat outdated due to the shifting demographics and activity patterns of the California population (Wiley, 1991a; Wiley, 1991b; DPR, 2000b).

   a. In both surveys, the target population of “English-speaking California residents….in households with a telephone” specifically excluded non-English speaking households and those without a telephone. As noted in the draft RCD (page 165) the Wiley studies were also “generic” in the sense that they targeted a state-wide population, but may not accurately represent the Merced County community. A 2003-2004 survey of California farmworkers found that 53% spoke no English and 42% earned less than $10,000/year (Aguirre International, 2005), suggesting that the survey results may not be representative of communities which include a significant number of farmworkers.

   b. The high mobility scenario used in the HEE5CB exposure simulation appears to vary the “home” and “away from home” townships, but the draft RCD did not clearly define these assumptions, so it was difficult to distinguish between the high and intermediate scenarios. Please clarify these basic assumptions.
2. OEHHA agrees with the DPR assessment of the average and lifetime residency durations that were determined in the Kaplan survey (Driver et al, 2014) as both values approach the typically-assumed default values for residential exposure.

OEHHA recommends that DPR address the following issues in the draft RCD:

- The Kaplan survey methods and MCABLE model have not been formally examined by external scientific peer review. Margin of error in the survey results was not provided.

- Based on the registrant’s sensitivity analysis, two factors (simulated air concentrations and residency-mobility) were discussed in greater detail for the lifetime ambient estimates. The registrant’s sensitivity analysis suggested that several model parameters have a relatively minor effect on the exposure estimates. We suggest adding a discussion on the direction and magnitude of these parameters individually, as well as their cumulative effect.

3. OEHHA has the following concerns regarding estimation of lifetime ambient air exposure:

- The Kaplan residential survey used in the MCABLE analysis only surveyed adults (age 18 and older). Although one might assume that some of the longer ambient exposure estimates would include childhood exposure, it is not clear how the higher exposures from birth through age 17 were factored into the MCABLE analysis.

- Exposure to carcinogens during early life stages is considered to be a major risk factor for cancer later in life (Carpenter et al. 2013). Exposure for several age groups (women in their third trimester of pregnancy, birth to 2 years old, 2 years to 16 years old and adults age 16 to 70 years old) should be estimated separately to allow for the application of age-sensitivity factors in the calculation of cancer risk (OEHHA, 2009).

- MCABLE also varies the “start age” – the age at which exposure begins instead of the birth-to-30 or birth-to-70 assumptions. Using the MCABLE model, cancer risk estimates for the portion of the population that is only exposed as adults would be lower than the birth-to-30 population because age-adjustment factors that account for enhanced sensitivity during childhood would not be factored in. For this reason, OEHHA does not support the use of the MCABLE model for estimating health risks.

4. OEHHA recommends that DPR should use the 70-year lifetime exposure estimate as calculated by HEE5CB as this model uses standard assumptions for lifetime exposure.
H. Risk Characterization

1. Targets for Acceptable Exposure

For non-cancer local and systemic effects, for adults, the target MOE of 30 was calculated based on an UF of $\sqrt{10}$ for interspecies pharmacodynamics (PD) and 10 for intraspecies variability. For children, an additional UF of 3 was added due to database uncertainty, resulting in a target MOE of 100.

As discussed in the section under Uncertainty Factors, OEHHA disagrees with the reduction of the interspecies pharmacokinetic UF of $\sqrt{10}$ to 1, and instead, advises an UF of 2 be retained for pharmacokinetic processes involved in systemic effects. In addition, OEHHA recommends an UF of 10 for intraspecies pharmacokinetics which would address the concerns for children as well as other sensitive subpopulations. These suggestions would result in the total UF, which is the magnitude of MOE required for acceptable exposure, as summarized in Table 9.

<table>
<thead>
<tr>
<th>RGDR approach</th>
<th>Interspecies PK</th>
<th>Interspecies PD</th>
<th>Intraspecies PK</th>
<th>Intraspecies PD</th>
<th>Total UF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local effect</td>
<td>1</td>
<td>$\sqrt{10}$</td>
<td>10</td>
<td>$\sqrt{10}$</td>
<td>100</td>
</tr>
<tr>
<td>Systemic effect</td>
<td>2</td>
<td>$\sqrt{10}$</td>
<td>10</td>
<td>$\sqrt{10}$</td>
<td>200</td>
</tr>
</tbody>
</table>

PK=pharmacokinetic, PD=pharmacodynamic

2. Targets for Cancer Risk

Despite the strong support for the non-threshold mechanism, the draft RCD also provided cancer risk estimates in terms of MOEs based on the threshold mechanism. There is no scientific basis for the proposed target MOEs of 300 to 1000 to evaluate cancer risk. Thus it is OEHHA’s opinion that it is inappropriate to make conclusions about acceptable cancer risk based on the threshold MOA assumption.

For oncogenic risk, OEHHA agrees with the use of the de minimus risk of $1 \times 10^{-6}$ as the negligible risk for the evaluation of carcinogenicity. However, OEHHA recommends that the calculated risks for residents should include age-sensitivity factors. In addition, the discussion of cancer risks from 1,3-D exposure should include consideration of co-exposure to chloropicrin.
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1,3-Dichloropropene
Review of DPR Draft RCD

OEHHA
November 2015


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