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DATE: August 6, 2016

SUBJECT: Response to comments by OEHHA on DPR-HHAB's draft 1,3-dichloropropene risk assessment document (dated August 31, 2015)

Responses to OEHHA comments on HHAB's draft 1,3-dichloropropene RCD (dated Aug. 31, 2015)

OEHHA submitted comments pertaining to HHAB's draft 1,3-D risk characterization document in a memorandum entitled: "Pesticide Exposure and Risk Assessment Peer Review – Document Review: Department of Pesticide Regulation's Draft Risk Characterization Document for 1,3-Dichloropropene" dated November 24, 2015 (OEHHA, 2015). The following paragraphs provide DPR-HHAB's responses to each of the comments as they appear in OEHHA's "Summary of Review" and "Response to Charge Questions" In addition, responses are presented to those substantive issues in the "Detailed Comments" section of OEHHA's document that were not otherwise covered in the "Summary of Review" and "Response to Charge Questions" sections.

I. SUMMARY OF REVIEW

A. Hazard Identification and Risk Characterization

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

OEHHA comment #1: OEHHA agrees with the critical endpoints selected for acute toxicity (body weight reduction), subchronic toxicity (respiratory epithelial hyperplasia), and chronic toxicity (respiratory epithelial hyperplasia).

DPR-HHAB response: No response necessary.

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OEHHA comment #2: 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.

DPR-HHAB response: DPR-HHAB agrees with OEHHA's comment. The critical endpoints (*i.e.*, points of departure, or PODs) for the subchronic and chronic exposure durations were reanalyzed and are now expressed as BMCLs (16 ppm and 6 ppm, respectively) in the revised RCD (dated Dec. 31, 2015).

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OEHHA comment #3: 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.

DPR-HHAB response: No response necessary.

OEHHA comment #4: 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.

DPR-HHAB response: See response to comment #2 above. Also, HHAB agrees with OEHHA that a benchmark response rate of 10% is appropriate to characterize the dose response for respiratory epithelial hyperplasia due to the mildness of that endpoint.

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2. Carcinogenicity identification and cancer potency determination

OEHHA comment #1: 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 U.S. EPA and the International Agency for Research on Cancer (IARC). 1,3-D is listed under Proposition 65 as a carcinogen.

DPR-HHAB response: No response necessary.

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OEHHA comment #2: 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.

DPR-HHAB response: A systemic mode of action can be supported by some of the published literature, including results from a National Toxicology Program study which showed induction of tumors in B6C3F1 mice at 50 and 100 mg/kg/day after 2 years (NTP 1985). However, DPR recently reviewed one additional study that provides limited support for a portal of entry mode of action vis a vis the inhalation-induced bronchioloalveolar tumors. Received by

DPR in April 2016, Kelly (1997) showed that oral gavage exposure of CD-1 mice to 1,3-D up to a high dose of 25 mg/kg/day for 18 months did not result in lung tumors. This is in contrast to the NTP (1985) study, which showed induction of these tumors in B6C3F1 mice at 50 and 100 mg/kg/day after 2 years. The NTP study lasted 2 years as opposed to 18 months for Kelly (1997) and it also utilized a different mouse strain and exposed the animals to higher doses. However, the Registrant (DowAgro Sciences) argues (1) that tumor induction in the NTP study was due to the presence of the mutagenic stabilizing agent epichlorohydrin in the administered 1,3-D formulation, and (2) that the absence of lung tumors in Kelly shows that inhalation exposure (that is, portal of entry) is required.

Because of these new data and consideration of the weight of evidence, our view remains that portal of entry is the more plausible mode of action for 1,3-D. The revised RCD contains oncogenic risk calculations and a discussion of the weight of evidence for a portal of entry *vs.* a systemic mode of action with respect to induction of bronchioloalveolar adenomas in male mice. This discussion in the revised RCD (pages 117-118), is quoted here:

> For multistage dose modeling, the air concentrations used in the mouse study were converted to human equivalent concentrations (HECs) assuming two different mechanistic scenarios: (1) adenomas arose following direct interaction of inspired 1,3-D with the tracheobronchial and pulmonary epithelial surfaces of the lung. This portal-of-entry scenario would be similar to the subchronic and chronic induction of nasal epithelial hyperplasia, but requiring a much higher RGDR to compute an HEC because the ratio of minute volume to involved respiratory system surface area was much less for humans than for mice; and (2) adenomas arose following absorption and circulatory redistribution to the lung of 1,3-D or its metabolites. As the second scenario invokes systemic exposure, dose scaling from mouse to human utilized a default RGDR of 1, similar to our treatment of acute toxicity. We chose to characterize lung tumorigenesis in both ways because the data did not point overwhelmingly to one or the other scenario, though we felt ultimately that the evidence tilted to the portal of entry scenario. The following observations were marshalled in support of portal of entry: (a) upper respiratory irritation occurred after acute, subchronic and chronic exposure in rodents (Cracknell *et al.*, 1987; Nitschke *et al.*, 1990) and after acute exposure in humans (section III.B.1. above); in addition, rats decreased their breathing rate at 90 ppm (Stott and Kastl, 1986), which was interpreted as evidence for sensory irritation in the upper respiratory tract; (b) pharmacokinetic studies in rats showed definitively that

inspired 1,3-D reaches the lower respiratory system (Stott and Kastl, 1986); (c) 1,3-D causes tumors on contact in other mouse tissues, including forestomach upon gavage exposure and skin (papillomas) upon dermal exposure (NTP, 1985); (d) skin sensitization resulted after dermal exposure in guinea pigs (Jeffrey, 1987); (e) oral, but not inhalation, exposure in rats caused liver adenomas, suggesting that local mechanisms were operative for liver tumors (Stott *et al.*, 1995). Supporting a systemic scenario is the following evidence: (a) 1,3-D is readily absorbed by the inhalation route in both rats (Stott and Kastl, 1986) and humans (Waechter *et al.*, 1992); (b) inhalation exposure leads to epithelial hyperplasia in the mouse bladder (Stott *et al.*, 1987) and, at higher concentrations, histopathologic changes in the kidneys, stomach and liver; (c) oral exposure in mice caused bronchioloalveolar tumors similar to those developing from inhalation exposure, suggesting that even by the inhalation route, absorption might be required for tumor development (NTP, 1985), though it is also possible that oral dosing led to inhalation exposure through reflux of volatilized or non-volatilized 1,3-D (Sells *et al.*, 2007; Damsch *et al.*, 2011a; Damsch *et al.*, 2011b).

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OEHHA comment #3: 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.

DPR-HHAB response: Regarding OEHHA's first point ("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"), while representing only a very minor difference from the enumeration used by HHAB, we stayed with the original approach in the revised RCD. OEHHA assumes that because the first decedent to be detected with a bronchioloalveolar tumor died on test day 558 (high dose animal #84A0550), that it took at least that long for such a tumor to develop. A consequence of this decision is that one 5-ppm animal dying at 547 days (animal #84A0388) WITHOUT a bronchioloalveolar

adenoma should not be considered "at risk". However, we believe the latter animal may in fact be at risk---it just didn't have a BA adenoma---and should be included in the "at risk" category. Our practice of excluding only those animals that died before 1 year (2 animals---one at 0 ppm and one at 20 ppm) is more defensible since they are much more likely NOT to be at risk.

Regarding OEHHA's second point ("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"), we note first that the RCD---both the draft and the final version---summarizes all studies that produced tumors, whether by the inhalation route or any other route. This was done in order to support the more general point that 1,3-D is a carcinogen. That said, we did not feel that potency analyses on the relevant oral and dermal studies were called for because those exposure routes were unlikely to influence the interpretation of the (route specific) inhalation-induced tumors.

Regarding OEHHA's third point ("perform multisite tumor analysis when appropriate"), we did not carry out multisite analysis because the route specific mouse study was sufficient. Adding other studies into the mix was likely to increase the uncertainty of our analysis.

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3. Interspecies extrapolation

OEHHA comment #1: 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.

DPR-HHAB response: No response necessary.

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OEHHA comment #2: OEHHA disagrees with the reduction of the intraspecies pharmacokinetic uncertainty factor (UF) from a value of √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.

DPR-HHAB response: First, as a clarification, we reduced the *inter*species (not intraspecies) pharmacokinetic UF to 3 (rounded from √10). In so doing, we followed the direction of U.S. EPA as stated in their 1994 position paper, page 4-78:

> "For derivation of the RfC, the UF applied for interspecies extrapolation… is 3 due to the incorporation of dosimetric adjustments. If more rigorous adjustments can be made, an additional reduction of the UF would be warranted. The threefold factor represents the reduction of the usual 10-fold factor by half (*i.e.,* $10^{0.5}$) since the default dosimetry accounts for variability in disposition (pharmacokinetics). The residual uncertainty is envisioned to address species differences in pharmacodynamics."

"Dosimetric adjustments" in this case would include the RGDR-derived human equivalent concentrations calculated in the 1,3-D RCD. The use of $10^{0.5}$ to characterize pharmacodynamics uncertainty is consistent with previous DPR risk assessment guidance. No further adjustment for pharmacokinetic uncertainty was considered necessary.

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OEHHA comment #3: For the lung tumors found in mice, OEHHA recommends the use of the body weight scaled to the ¾ 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.

DPR-HHAB response: As noted above, we agree at least to some extent with OEHHA's assertion that "the lung cancer is [not] strictly a portal of entry effect". For that reason, we have included risk calculations for both a portal of entry and a systemic mode of oncogenic action in the revised RCD. Even so, we continue to hold that the evidence tilts toward a portal of entry mechanism (see response to comment #2, section 2 above). However, our calculations using RGDR-derived human equivalent concentrations suggest that the oncogenic potency for non-workers of 0.018 $(ppm)^{-1}$ is only 3.6-fold lower than OEHHA's value of 0.05 $(mg/kg)^{-1}$ if a portal of entry mechanism is assumed, not 24-fold lower as asserted by OEHHA. In addition,

when we assume a systemic mode of action, our oncogenic potency of 0.062 $(ppm)^{-1}$ is equivalent to OEHHA's value. These calculations are as follows:

Portal of entry
0.018 $(ppm)^{-1}$ = 0.004 $(mg/m^3)^{-1}$ *i.e.*, using the 1,3-D conversion 1 ppm = 4.54 mg/m^3
0.004 $(mg/m^3)^{-1}$ ÷ 0.28 m^3/kg = 0.014 $(mg/kg)^{-1}$
0.05 $(mg/kg)^{-1}$ ÷ 0.014 $(mg/kg)^{-1}$ ≈ 3.6

Systemic
0.062 $(ppm)^{-1}$ = 0.0137 $(mg/m^3)^{-1}$ using the 1,3-D conversion 1 ppm = 4.54 mg/m^3
0.0137 $(mg/m^3)^{-1}$ ÷ 0.28 m^3/kg = 0.049 $(mg/kg)^{-1}$
0.05 $(mg/kg)^{-1}$ ÷ 0.049 $(mg/kg)^{-1}$ ≈ 1

These calculations suggest that for 1,3-D, the method of estimating oncogenic potency---be it RGDR dosimetry or body weight scaling to the ¾ power---is not critical. Rather, the assumption regarding mode of action---portal of entry *vs.* systemic---is the key consideration in the potency estimation.

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4. Intraspecies variation and sensitive populations

OEHHA comment #1: 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).

DPR-HHAB response: We assumed a default intraspecies factor of 10 that includes a pharmacokinetic UF of √10 and a pharmacodynamic UF of √10. This is in agreement with the approach taken by U.S. EPA both in their 2007 health assessment and their 2013

scoping document on 1,3-D (U.S. EPA, 2013) . For children, the HHAB differed from U.S. EPA in that we applied an additional database UF of 3.

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OEHHA comment #2: 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.

DPR-HHAB response: The concern for potential increased cancer susceptibility due to early childhood exposure to carcinogens is addressed using age-sensitivity factors (ASFs). The recommended ASFs are: 10 (last trimester/birth up to 2 years old) and 3 (2 to < 16 years old). U.S. EPA applies ASF factors in the calculation of risks associated with carcinogens with a mutagenic MOA (U.S. EPA, 2005) and OEHHA applies it for all carcinogens regardless of mode of action (OEHHA, 2009). U.S. EPA provides several biological rationales for why the potency of mutagenic carcinogens might be greater if exposure occurs during early life stages. These include the following:

- Tissues from developmentally immature individuals, which are likely to contain large populations of dividing cells, may allow for the fixation and subsequent expansion of initiated cells before there is an opportunity for DNA repair.

- DNA repair enzyme levels may themselves be underdeveloped, lowering the likelihood that DNA damage will be repaired.

- Immune competence in the developing organism may be insufficient to clear abnormal cells.

- Developing hormonal systems may prime carcinogenic responsivity.

- Developmental anomalies induced by oncogens early in life may be prone to cancer, or at least susceptible to oncogenic induction by toxicants, later in life.

HHAB recognizes these issues and is currently updating its own risk assessment guidance, including guidelines for when it is appropriate to apply defaults for cancer risks to susceptible

subpopulations (including early life and other stages) and when departures from those defaults may be justified.

In this regard, HHAB relied on LADDs that took into account differences in breathing rates and body weights between adults and children when estimating cancer risks from 1,3-D inhalation exposures. While noting that further age-adjustment of the oncogenic risk is lacking in the RCD, we felt that the overall weight of evidence does not support imposition of ASF factors in this specific case. The position papers by U.S. EPA (2005) and OEHHA (2009) demonstrating increased early-life susceptibility for several oncogens and tumor types were entirely based on data from systemic studies by the oral, subcutaneous, or intraperitoneal routes. As such, they did not account for biological processes that may underlie portal of entry-based tumorigenesis by the inhalation route, thus assuming parity between systemic and portal of entry modes of action. Moreover, examination of the only data that we are aware of pertaining specifically to lung oncogenesis, acute exposures (albeit by systemic exposure) generated a mean child-to-adult potency ratio of 1.1, as opposed to other tissues which showed conspicuously higher values (U.S. EPA, 2005). For these reasons, we did not invoke ASFs for inhaled 1,3-D, considering that our linearized multistage-based air unit risk values were sufficiently conservative to protect all population groups. While these considerations provide a rationale for not applying ASFs at the current time, HHAB will revisit and evaluate this issue if more data become available.

Even so, if default ASFs <u>are</u> ultimately applied to estimate cancer risks over multiple life stages (infant, juvenile and adult for a portal of entry mode of action; 3rd trimester, infant, juvenile and adult for systemic mode of action), the age-adjusted risk for 1,3-D would increase by 1.7-fold compared to risk calculated for adult exposure. The Table below compares residential cancer risk from Summary Table III in the RCD (MCABLE, without time away, low mobility, birth to age 70) to age-adjusted risk for portal and entry and systemic modes of action.

Lifestage	Fractional duration	ASF	Potency [µg/kg/day]$^{-1}$	Oncogenic risk MACABLE	
				PoE	Systemic
Adult (not ASF-adjusted)	70 years	none	0.000014 (PoE) 0.000048 (systemic)	$4.66x10^{-6}$	$1.60x10^{-5}$
3rd Trimester/Infant	2.25 years / 70 years	10	0.000048 (systemic)	-	$5.72x10^{-7}$
Infant	2 years / 70 years	10	0.000014 (PoE) 0.000048 (systemic)	$1.33x10^{-6}$	$4.58x10^{-6}$
Child	14 years/70 years	3	0.000014 (PoE) 0.000048 (systemic)	$2.80x10^{-6}$	$9.61x10^{-6}$
Adult	54 years / 70 years	1	0.000014 (PoE) 0.000048 (systemic)	$3.59x10^{-6}$	$1.24x10^{-5}$
Total (ASF-adjusted)				$7.72x10^{-6}$	$2.72x10^{-5}$
Total (ASF-adjusted) ÷ Adult (not ASF-adjusted) = $(7.72x10^{-6}) \div (4.66x10^{-6}) = 1.7$ (PoE) **= $(2.72x10^{-5}) \div (1.60x10^{-5}) = 1.7$ (systemic)**					

Abbreviations: ASF, age-sensitivity factor; PoE, portal of entry
$ASF_{child} = 10$; $ASF_{juvenile} = 3$; $ASF_{adult} = 1$. Total (age-adjusted risk) is based on the following for formula:
For portal of entry MOA: [(2 yr ÷ 70 yr) x ASF_{child} x CR] + [(14 yr ÷ 70 yr) x $ASF_{juvenile}$ x CR] + [(54 yr ÷ 70 yr) x ASF_{adult} x CR]
For systemic MOA: [(2.25 yr ÷ 70 yr) x ASF_{child} x CR] + [(14 yr ÷ 70 yr) x $ASF_{juvenile}$ x CR] + [(54 yr ÷ 70 yr) x ASF_{adult} x CR] = lifetime non-occupational cancer risk
CR = cancer risk

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5. Risk characterization

OEHHA comment #1: OEHHA recommends a re-evaluation of the target margin of exposure (MOE) 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.

DPR-HHAB response: These considerations were handled in several responses above.

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OEHHA comment #2: OEHHA agrees with the use of the *de minimus* risk of 1 x 10^{-6} as the target to compare calculated human cancer risks.

DPR-HHAB response: No response necessary.

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B. Exposure Assessment

1. Occupational exposure

OEHHA comment #1: 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.

DPR-HHAB response: There are no exposure data specific to "maintaining or adjusting equipment". However, the exposure data for the applicator and loader exposure scenarios include activities, such as connecting or disconnecting lines and transferring the product via pumps, associated with loading and applying the product.

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OEHHA comment #2: 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.

DPR-HHAB response: Due to a lack of data, chloropicrin surrogate data were used to derive 1,3-D air concentrations for certain exposure scenarios. For detailed investigation of the chloropicrin data, references to a memo reviewing the chloropicrin studies and to the studies themselves were included in the references section of the RCD. The review considered several factors that could potentially impact occupational exposures in the studies, including soil type, soil moisture, and percent organic matter (tarp type and thickness did not appear to differ between studies). No factor was found to consistently contribute to differences in exposures between studies (Beauvais, 2010).

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OEHHA comment #3: 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.

DPR-HHAB response: The following text concerning the use of chloropicrin data was included in the latest draft of the RCD:

"The surrogate ratio approach using chloropicrin is a reasonable first approximation of the 1,3-D worker breathing zone air concentrations. Chloropicrin and 1,3-D do differ in their physical and chemical properties, and those differences produce differing patterns in mass loss following the application. However, both chloropicrin and 1,3-D tend to show small flux immediately following the application. For the majority of applications the maximum flux for both chloropicrin (Barry, 2014) and 1,3-D (Knuteson, 1992b; Knuteson, 1992a; Knuteson *et al.*, 1995; Gillis, 1998; Knuteson and Dolder, 2000; van Wesenbeeck and Phillips, 2000) occur 6 or more hours following application. In some studies the maximum flux occurs 24 hours or more following the application. During the application process the magnitude of flux will more likely be dominated by the application method itself. Application methods are reasonably standard between fumigants. The similarly small initial flux for most chloropicrin and 1,3-D applications supports this assumption and by extension, also supports the surrogate ratio approach.

The applicability of the chloropicrin tarp remover surrogate ratio depends upon the permeability of the tarps used and the soil degradation rate of chloropicrin relative to 1,3-D. U.S. EPA conducted analysis of laboratory measured tarp permeability for various tarp types (Sarkar, 2010). Those results indicate that for 25 tarps, chloropicrin permeability is lower than 1,3-D permeability. Chloropicrin and 1,3-D differ in their soil degradation rate, 3.5 days versus 7 days, respectively (Johnson, 2012). However, modeling analysis conducted with the HYDRUS soil physics model indicates that chloropicrin and 1,3-D 6-hr flux were within a factor of 2 for both a 5 day and a 10 day tarp cutting interval (Johnson, 2012). Thus, for tarp remover exposure scenarios chloropicrin is a reasonable 1,3-D surrogate."

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OEHHA comment #4: 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.

DPR-HHAB response: In the final draft of the RCD, all five observations were used for estimating exposure.

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OEHHA comment #5: 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.

DPR-HHAB response: The current practice at the Human Health Assessment (HHA) branch is to use the Maximum Likelihood Estimate (MLE) of estimation for short-term exposure estimates (Frank, 2009b). The divisor of the Sum of Squares to obtain the MLE is (n) not (n-1).

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2. Residential Exposure

OEHHA comment #1: 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.

DPR-HHAB response: The comment is valid and there is a possibility that residents are exposed to 1,3-D at distances less than 100 feet from an application site. The following text was added to the Exposure appraisal section on page 186 of the revised RCD:

> "The majority of 1,3-D product labels and CA permit conditions for products containing chloropicrin, mandate a 100-foot buffer zone between the fumigated field and occupied structures. All but three labels (Telone EC, Telone II and TriCal Trilone II) also require that all non-handlers, including field workers, residents, pedestrians, and other bystanders, must be excluded from the buffer zone during the buffer zone period. These 3 labels allow the possibility that residents spending time outdoors are within the limits of the buffer zone. These residents would experience 1,3-D exposure higher than the residential bystander exposures presented in this document for the edge of the buffer zone. Although we expect such exposures to be rare and short in duration (up to several hours), the possibility of accidental acute bystander exposures of this kind remains. These exposures will approximate the occupational bystander exposures outlined in Table IV.8 (Occupational Exposure Estimates) and will be in the range of 0.6-2.0 ppm for an 8-hr exposure, depending on the application method".

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OEHHA comment #2: 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.

DPR-HHAB response: We agree with OEHHA that MCABLE has not undergone external scientific review; however, as stated in page 165 of the draft RCD, the consistency in model outputs between HEE5CB and MACBLE suggests that these models can provide a valuable insight into the range of exposures and oncogenic risks associated with the use of 1,3-D in California.

OEHHA's recommendation is based on the premise that 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 may exhibit different sensitivities to 1,3-D. However, as noted in U.S. EPA's guidance document on this issue (U.S. EPA, 2005), there is no clear evidence of age-related sensitivity associated with chemicals that induced lung tumors. Also, as indicated in the RCD (page 102), results of 1,3-D reproductive and developmental toxicity studies did not show evidence of age-related increases in sensitivity. Nevertheless, age-specific differential sensitivity to airborne toxicants such 1,3-D is plausible due to differences in physiology such as body weight and breathing rates. In conducting the stochastic human exposure simulations, age-specific inhalation rates and body weights were used. But in the end, even after all of these considerations were taken into account, we were left with the possibility that lung tissue in the developing human was more sensitive to the oncogenic influence of 1,3-D. We discuss this possibility above (section 4, response to comment 2).

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II. RESPONSE TO CHARGE QUESTIONS

A. Hazard Identification and Risk Characterization

Risk assessment 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.

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

DPR-HHAB response: No response necessary.

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Risk assessment 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.

OEHHA 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.

DPR-HHAB response: No response necessary.

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Risk assessment 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.

OEHHA 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.

DPR-HHAB response: Our view is summarized above in the response to OEHHA comment #2, section 3 (Interspecies extrapolation).

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Risk assessment 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.

OEHHA 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.

DPR-HHAB response: No response necessary.

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Risk assessment 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---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.

OEHHA 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.

DPR-HHAB response: No response necessary.

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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

OEHHA 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.

DPR-HHAB response: See response to comment #2 in Section B.1 (Exposure Assessment; Occupational Exposure).

■ 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.

DPR-HHAB response: See response to comment #3 in Section B.1 (Exposure Assessment; Occupational Exposure).

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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.

OEHHA 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 under prediction. 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.

DPR-HHAB response: See response to comment #2 under Section B.2 (Exposure Assessment; Residential 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.

DPR-HHAB response: See response to comment #2 under Section B.2 (Exposure Assessment; Residential Exposure).

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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.

OEHHA 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.

DPR-HHAB response: See response to comment #1 under Section B.2 (Exposure Assessment; Residential Exposure).

III. SUBSTANTIVE ISSUES RAISED IN THE "DETAILED COMMENTS" SECTION OF THE OEHHA CRITIQUE

E. Carcinogenicity Weight of Evidence

5. Co-exposure to chloropicrin

OEHHA comment (page 17): 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.

DPR-HHAB response: DPR is requiring additional data from chloropicrin registrants to obtain more information on the potential carcinogenicity of chloropicrin. Assessment of risks from co-exposure to chloropicrin and 1,3-D is not feasible given the available data and current state of risk assessment science. In its groundbreaking 2008 report on cumulative risk assessment, the National Academy of Sciences (NAS) Committee on the Health Risks of Phthalates advocated assessment of cumulative risks from mixtures of dissimilar chemicals with similar health effects (NAS, 2008). However, the NAS Committee also recognized several scientific issues including lack of evidence of combined effects at low (environmentally relevant) doses for most mixtures (which is the case for 1,3-D and chloropicrin) and insufficient information to determine the most valid approach to quantitate

risk. For example, dose additivity is an appropriate assumption for chemicals having a similar mode of action, but not for chemicals with dissimilar modes of action. For example, dose additivity is an appropriate assumption for chemicals having a similar mode of action, but not for chemicals with dissimilar modes of action. Furthermore, use of a relative potency approach to combined estimates of risk requires a constant proportion of effect to dose throughout the dose range being considered. This information is not available for 1,3-D and chloropicrin.

G. Exposure Assessment

1. Handler exposure estimates

OEHHA comment #1 (page 21): 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.

DPR-HHAB response: The 1,3-D data obtained with spillage controls in place were used for the shank applicator scenarios because, according to the product labels, spillage controls are required for shank application in CA.

The high exposure potential activities were not excluded from the draft RCD. The sampling data used to estimate exposure included high exposure potential activities along with other activities associated with the scenario. The samples were the longest (4-hr TWA), taken in the study and were deemed more representative of the actual exposures a worker may experience over the default work period used for estimating exposure (i.e., 8-hrs/day).

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OEHHA comment #2 (page 21): 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 (Frank, 2009b).

DPR-HHAB response: In the final draft of the RCD, all five observations were used for estimating exposure.

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OEHHA comment # 3 (page 21): 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).

DPR-HHAB response: The current practice at the Human Health Assessment (HHA) branch is to use the Maximum Likelihood Estimate (MLE) of estimation short-term exposure estimates (Frank, 2009a). Hence, (n-1) is not an appropriate divisor for the Sum of Squares as dictated by this method.

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OEHHA comment #4 (page 21): 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. The same surrogate chemical assumption was subsequently applied to 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).

DPR-HHAB response: The following text concerning the use of chloropicrin data was included in the latest draft of the RCD:

> "The surrogate ratio approach using chloropicrin is a reasonable first approximation of the 1,3-D worker breathing zone air concentrations. Chloropicrin and 1,3-D do differ in their physical and chemical properties, and those differences produce differing patterns in mass loss following the application. However, both chloropicrin and 1,3-D tend to show small flux immediately following the application. For the majority of applications the maximum flux for both chloropicrin (Barry, 2014) and 1,3-D (Knuteson, 1992b; Knuteson, 1992a; Knuteson *et al.*, 1995; Gillis, 1998; Knuteson and Dolder, 2000; van Wesenbeeck and Phillips, 2000) occur 6 or more hours following application. In some studies the maximum flux occurs 24 hours or more following the application. During the application process the magnitude of flux will more likely be dominated by the application method itself. Application methods are reasonably standard between fumigants. The similarly small initial flux for most chloropicrin and 1,3-D applications supports this assumption and by extension, also supports the surrogate ratio approach.
>
> The applicability of the chloropicrin tarp remover surrogate ratio depends upon the permeability of the tarps used and the soil degradation rate of chloropicrin relative to 1,3-D. U.S. EPA conducted analysis of laboratory measured tarp permeability for various tarp types (Sarkar, 2010). Those results indicate that for 25 tarps, chloropicrin permeability is lower than 1,3-D permeability. Chloropicrin and 1,3-D differ in their soil degradation rate, 3.5 days versus 7 days, respectively (Johnson, 2012). However, modeling analysis conducted with the HYDRUS soil physics model indicates that chloropicrin and 1,3-D 6-hr flux were within a factor of 2 for both a 5 day and a 10 day tarp cutting interval (Johnson, 2012). Thus, for tarp remover exposure scenarios chloropicrin is a reasonable 1,3-D surrogate.

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OEHHA comment #5 (page 21): 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.

DPR-HHAB response: Due to a lack of data, chloropicrin surrogate data were used to derive 1,3-D air concentrations for certain exposure scenarios. For detailed investigation of the

chloropicrin data, references to a memo reviewing the chloropicrin studies and to the studies themselves were included in the references section of the RCD.

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OEHHA comment #6 (page 21): 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.

DPR-HHAB response: Some confusion may have occurred due to the mistaken omission of a critical reference describing the 95th %-ile approach (Frank, 2009c). This reference will be added to the final draft of the RCD.

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OEHHA comment #7 (page 21): 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.

DPR-HHAB response: The 1,3-D data obtained with spillage controls in place were used for the shank applicator scenarios because, according to the product labels, spillage controls are required for shank application in CA.

The high exposure potential activities were not excluded from the draft RCD. The sampling data used to estimate exposure included high exposure potential activities along with other activities associated with the scenario. The samples were the longest (4-hr TWA), taken in the study and were deemed more representative of the actual exposures a worker may experience over the default work period used for estimating exposure (i.e., 8-hrs/day).

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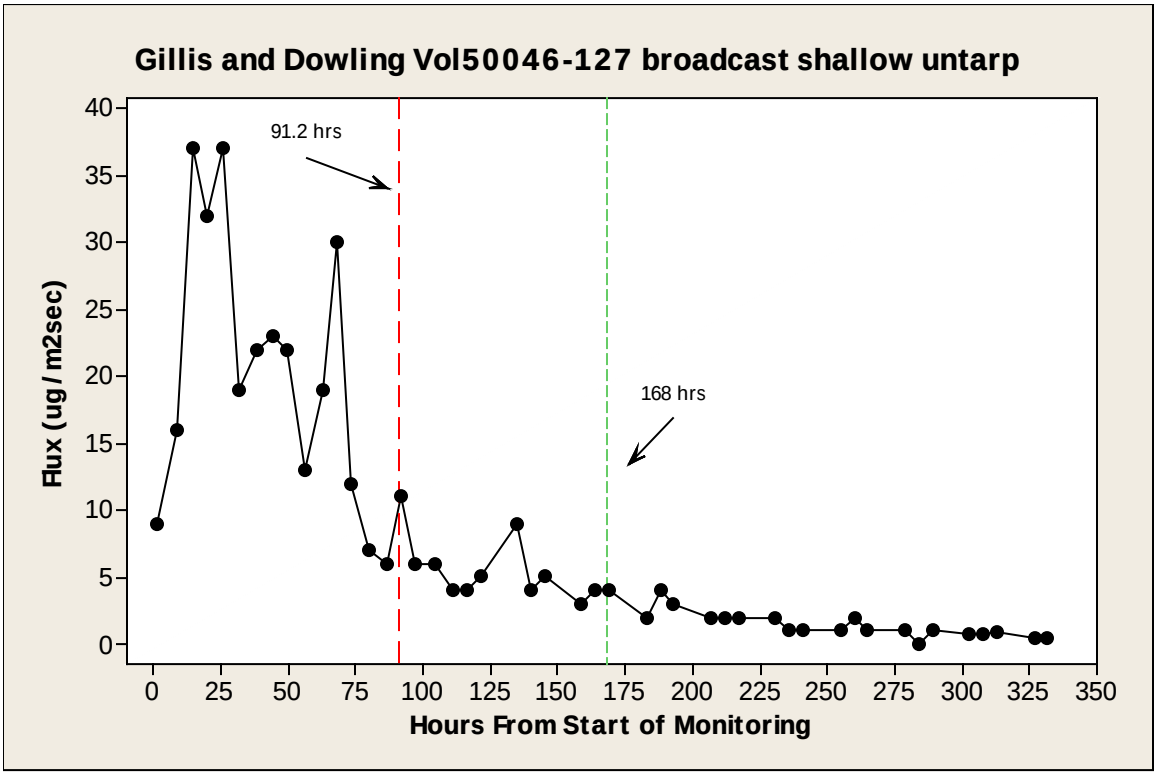
OEHHA comment #8 (page 22): OEHHA recommends that DPR (1) clarify why some activities can take place before the end of the REI and (2) estimate the uncertainty in using a study conducted 3.8 days post-fumigation as representative of all reentry activities.

DPR-HHAB response: Certain activities, such as tarp removal, are allowed to occur prior to the expiration of the REI because product labels and CA permit conditions allow them.

The uncertainty(s) can be estimated by describing the variables encountered when calculating the 1,3-D fluxes at 3.8 vs. 7 days after application. To describe these variables, the 1,3-D flux profile of a field (Field 1), treated using broadcast shallow shank without the use of a soil-sealing tarp was examined (Gillis, 1998).

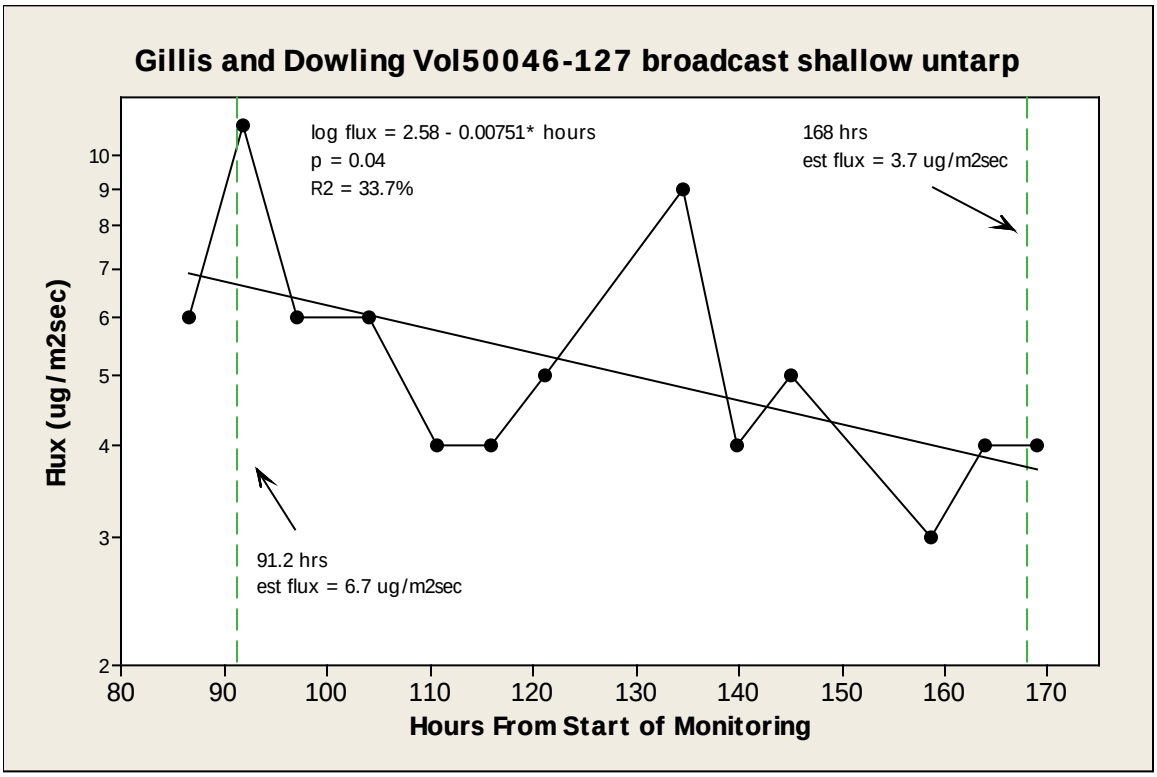
Below is a plot of the entire measured flux profile with 0 hrs being the beginning of flux sampling and each flux shows at the end of each respective sampling interval. The application ended shortly before the flux sampling began but the exact time was not provided.



The general pattern of the flux profile is exponential decline after the first peaks are reached at 15 and 37 hrs. However, it is clear that fitting that exponential would be difficult to impossible. TableCurve® software was used to fit the decline and, as expected, no acceptable fit could be found. There is a decline but fitting a single viable function is impossible. The interval between 3.8 days (91.2 hrs) and 7 days (168 hrs) is shown as vertical lines. It is clear that the flux values in this interval are not monotonically decreasing. However, it appears it is likely that the flux at 91.2 hrs is numerically larger than the flux at 168 hrs. This does not mean the flux between those two time points are statistically different.

Flux is only one of the variables that produce air concentrations to which workers will be exposed. Although it is true that in air dispersion modeling that air concentrations are directly proportional to flux, that is *with all other factors held constant*. So, the uncertainty in differences in meteorology between these two time points should be considered. In addition, if the air concentrations associated with these flux values were modeled using an air dispersion model, it should be noted that air dispersion models are considered to generally produce air concentrations within a factor of 2 of the actual air concentrations generated by that flux.

Regression analysis of the portion of the entire flux profile that falls between 86.6 hrs and 168 hrs is shown below. The regression is statistically significant, showing $p = 0.04$ for the slope. The $R^2 = 33.7\%$. While the regression is statistically significant it is clear that the linear function fits poorly. The estimated fluxes are 6.7 ug/m^2sec and 3.7 ug/m^2sec for 91.2 hrs and 168 hrs, respectively. The ratio of 3.7 to 6.6 is 0.55. So, the flux at 91.2 hrs is slightly less than double the flux at 168 hrs.



In summary, uncertainty is created by the lack of a monotonically decreasing flux profile in the area of interest (91.2 hrs to 168 hrs), the resulting poor fit of the regression, and the air dispersion model factor of two acceptability. Another potential source of uncertainty is the analytical variability of the study.

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OEHHA comment #9 (page 23): 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.

DPR-HHAB response: Worker exposure monitoring includes routine activities, such as connection and disconnection of fumigant tanks and flushing of equipment, and these activities are included in applicator exposure estimates. Risk assessment is not the appropriate

mechanism for addressing accidental overexposures like those reported to DPR's Pesticide Illness Surveillance Program. Accidental overexposures are addressed through enforcement.

2. Occupational bystander exposure estimates

OEHHA comment #10 (page 23): 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, 2012). 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.

DPR-HHAB response: In the first draft of the RCD, the air concentrations measured in Receptor 5, the receptor with the highest measured air concentrations in the aforementioned Merced County study, were used to estimate seasonal exposure. The mean of the air concentrations in this receptor measured during the 8-month use season for Fresno County, the highest use county from 2008-12, was made equal to the SAC. However, the township caps for 1,3-D were exceeded in the Merced County study. To address this issue, in the final draft of the RCD, the measured air concentrations from all 9 receptors in the Merced County study were used to estimate seasonal exposure. Specifically, the SAC was made equal to the mean of these air concentrations measured over the course of a modified use season for Merced County during the calendar year of the study (2011). This modified use season consists of the months during the estimated use season where the number of pounds of 1,3-D applied were less than those applied in the corresponding months in a higher use county for the same year (*i.e.*, Fresno County).

3. Residential bystander exposure estimates (edge of buffer zone)

OEHHA comment #11 (page 25): STAC [short-term air concentration] 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?

DPR-HHAB response: Most 1,3-D product labels state that the product shall not be applied to soil more frequently than once per year. Three labels lack this restriction: Telone II CA, Tri-Cal Trilone II, and Telone EC. However, the current agricultural practice indicates that fields are fumigated once a year or less. Strawberries are the leader of 1,3-D use among the annual crops (Table II.6 in the final RCD). According to the staff from Pest Management & Licensing Branch of DPR and UC Cooperative Extension-Santa Cruz County, "Most though not all strawberry fields for both transplants and production are typically fumigated once per year. Regarding rotations, as strawberries are generally grown on high value land, they tend to be rotated with other high value crops such as lettuce, artichoke and cole crops (e.g. broccoli). Growers will generally use a two year rotation, fumigating the first year, planting strawberry, then plant one of the vegetable crops the second year. (They do not fumigate the year they plant the vegetable crop.) About half of the growers rotate with a vegetable crop and the other half plant strawberry every year (and usually, but not always fumigate)".

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OEHHA comment #12 (page 25): 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 (Gao *et al.*, 2009; Kim *et al.*, 2013). 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.

DPR-HHAB response: We agree that the fields continue to off-gas past the 14th day post-application as indicated by registrant fumigation studies (Knuteson *et al.*, 1995; Knuteson and Dolder, 2000). The long-term 1,3-D flux was modeled for two weeks for consistency with a previous fumigant exposure assessment (Beauvais, 2012).

In their 1,3-D human health risk assessment (U.S. EPA, 2007) U.S. EPA acknowledged that the current state of science does not allow for modeling of cumulative exposures from neighboring fumigant applications. We concur with this view.

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OEHHA comment #13 (page 25): 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.

DPR-HHAB response: The comment is valid, and there is a possibility that residents are exposed to 1,3-D at distances less than 100 feet from an application site. The following text was added to the Exposure appraisal section on p. 186 of the final RCD: "The majority of 1,3-D product labels and CA permit conditions for products containing chloropicrin, mandate a 100-foot buffer zone between the fumigated field and occupied structures. All but three labels (Telone EC, Telone II, and TriCal Trilone II) also require that all non-handlers, including field workers, residents, pedestrians, and other bystanders, must be excluded from the buffer zone during the buffer zone period. These three labels allow the possibility that residents spending time outdoors are within the limits of the buffer zone. These residents would experience 1,3-D exposure higher than the residential bystander exposures presented in this document for the edge of the buffer zone. Although we expect such exposures to be rare and short in duration (up to several hours), the possibility of accidental acute bystander exposures of this kind remains. These exposures will approximate the occupational bystander exposures outlined in Table IV.8. (Occupational Exposure Estimates) and will be in the range of 0.6-2.0 ppm for an 8-hr exposure, depending on the application method."

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OEHHA comment #14 (pages 26-27): 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" (U.S. 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.

DPR-HHAB response: The SOFEA-2 model incorporated the new mixing height adjustment algorithm developed by DowAgroSciences. This mixing height adjustment starts with setting a windspeed that is less than 1.0 m/s equal to 1.0 m/s. So, that calm hour is not dropped, unlike the calms processing routine in the ISCST3 model. The mixing height is then adjusted according to the time of day, wind speed, and air temperature. This process allows a more complete accounting of the effect of low winds speeds on air concentrations. The frequency of calm conditions before the wind speed adjustment to 1.0 m/s can be conducted and would present additional information on the frequency and distribution of calm hours during the meteorological record.

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OEHHA comment #15 (page 27): 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?

DPR-HHAB response: The long dark hours, very stable atmospheric conditions, fog, low wind speeds, and overcast skies present during the winter months are accounted for in the modeling through the meteorological data. Specifically, the low wind speed and stable-to-very-stable atmospheric stability parameters present during more stable atmospheric conditions that are used in the Gaussian model to estimate air concentrations and will produce a more concentrated and narrower plume. This means that the cross-wind and vertical spread of the plume from an application will be damped, thus, the estimated air concentrations in the general vicinity of application sites will be higher than those estimated under more dispersive atmospheric conditions.

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OEHHA comment #16 (page 29): 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, 1991; Wiley *et al.*, 1991; CDPR, 2000). 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 [1]), suggesting that the survey results may not be representative of communities which include a significant number of farmworkers.

DPR-HHAB response: In theory, the health risk experienced by farmworkers working in a 1,3-D treated field should be higher than those living in a community with high 1,3-D use. Also, for the same farmworker who lived in the 1,3-D field and resided in a high 1,3-D use community, the added health risk of this farmworker should be the same as other residences resided in the same community due to the ambient exposure to 1,3-D. The potential health risk of farmworker associated with 1,3-D exposure has been addressed in the agricultural handler exposure assessment section; the health risks associated with various agricultural hander activities are 1-2 order of magnitude higher than the ambient exposure. Although the studies by Wiley *et al.* (1991) may have outdated and "generic" for use in stochastic human exposure modeling (i.e., HEE5CB), the same is not true for the residential mobility survey conducted by Kaplan (2014). That is, Kaplan's survey was conducted in 2013 in the two high 1,3-D use communities of Merced and Ventura. The survey results of Kaplan were incorporated into another stochastic human exposure assessment model (i.e., MCABLE). As stated in page 165 of the draft RCD, the consistency in model outputs between HEE5CB and MACBLE suggests that these models can provide a valuable insight into the range of exposures and oncogenic risks associated with the use of 1,3-D in California. Hence, we do not believe OEHHA concerns would constitute any material impact on our conclusion on 1,3-D cancer risk of farmworkers and non-farmworkers resided in a high 1,3-D use community.

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OEHHA comment #17 (page 29): 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.

DPR-HHAB response: The assumptions of "home" and "away from home" can be found in the draft RCD page 129.

[1] This reference, cited by OEHHA in the body of their text, did not appear in their bibliography.

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OEHHA comment #18 (page 30): 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.

DPR-HHAB response: MCABLE is currently undergoing peer-review by the U.S. EPA. Based on a sensitivity analysis conducted by the registrant (Driver *et al.*, 2014), simulated air concentrations and residency-mobility contributed 90% of the variation in LADD calculation for the cancer risk assessment. We have revised the text to clarify the importance of these variables.

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OEHHA comment #19 (page 30): 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 though age 17 were factored into the MCABLE analysis.

DPR-HHAB response: The mathematical procedure for compensating the effect of excluding younger individuals (i.e., <18 years old) in the survey has been detailed in the report by Driver *et al.* (2015)

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OEHHA comment #20 (page 30): Exposure to carcinogens during early life stages is considered to be a major risk factor for cancer later in life (Carpenter and Bushkin-Bedient, 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).

DPR-HHAB response: Age-specific sensitivity to airborne toxicants such 1,3-D is plausible due to differences in physiology such as body weight and breathing rates. Hence, in conducting the stochastic human exposure simulations, age-specific inhalation rates and body weights were used. Intrinsic tissue sensitivities may also exist. Age-specific adjustments to cancer risk are discussed in detail in section 4, comment 2 above.

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OEHHA comment #35 (page 30): 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. 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.

DPR-HHAB response: The purpose of performing the stochastic human exposure modeling such as MCABLE and HEE5CB is to inform the risk manager of the potential cancer risk associated with different exposure scenarios. The comment that "OEHHA does not support the use of the MCABLE model for estimating health risks" and that "DPR should use the 70-year lifetime exposure estimate as calculated by HEE5CB as this model uses standard assumptions for lifetime exposure" is noted.

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