Department of Pesticide Regulation

dpr

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FROM: Andrew L. Rubin, PhD, DABT *[original signed by A. Rubin]*
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DATE: November 8, 2016

SUBJECT: Response to comments by Dow AgroSciences on DPR-HHAB's draft 1,3-Dichloropropene Risk Characterization Document dated Aug. 31, 2015

Dow AgroSciences (DAS) submitted comments to the Human Health Assessment Branch of the Department of Pesticide Regulation (DPR-HHAB) on the draft 1,3-D Risk Characterization Document (RCD) in a memorandum dated October 16, 2015. This memorandum lists the DAS comments along with DPR-HHAB's detailed responses. The "revised RCD" referenced throughout this memo refers to the revised risk characterization document dated December 31, 2015. DAS comments appearing in the "Executive Summary" section are not answered in the current document because they appear in more complete form in the main body of the DAS memo.

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I.   SUMMARY

Draft RCD
Page # iv (Index)

DAS Comments:
Section V. Part B is followed by Part D.
Section V is followed by Section VII.

DPR-HHAB response: Agreed. Corrected in the revised RCD.

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Draft RCD
Page 1/Paragraph 3: "While the mechanism of pesticidal action is unclear, 1,3-D may work by inactivating vital enzymes through sulfhydryl or hydroxyl binding."

DAS Comments:
The "binding" is actually formation of covalent bonds due to nucleophilic displacement.

DPR-HHAB response: Agreed. The wording is amended in the revised RCD to reflect this point (p.1).

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Illness and injury reports

DAS Comments:
DPR's analysis of illness reports over the past 30 plus years confirms the low risk of acute exposures to 1,3-D, especially considering the amount of use in California during that time period. It would be helpful to put the number of alleged illness and injury reports into context with respect to the number of applications during those years. Less than 0.1% of applications resulted in a report of alleged injury or illness.

DPR-HHAB response: We did not consider it necessary to amend this section.

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Draft RCD
Page 1/Paragraph 5: "Of the 72 recently reported cases…" "Most of the cases involving 1,-D and…"

DAS Comments:
From 1998 to 2011 over 24,500 applications were made with only 5 reported cases from 3 episodes involving 1,3-D alone, representing less than 0.1% of all applications. It would be informative to the reader to include the low frequency of incidents in the summary.

DPR appropriately points out that most of the cases involving 1,3-D were confounded by the presence of other soil fumigants with known eye and respiratory irritants, thus 1,3-D was not likely to be the causative agent.

> **DPR-HHAB response:** We did not consider it necessary to amend this section.

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Pharmacokinetics

Draft RCD
Page 2/Paragraph 6: "This study showed rapid (less than a day) and complete uptake through the lung and subsequent metabolism to excretable compounds in humans."

DAS Comments:
Uptake is not "complete". Earlier in the same paragraph it says "…respiratory uptake was ~80% for both isomers". Eighty percent uptake is the value measured in both humans and rats.

> **DPR-HHAB response:** HHAB considers absorption levels of 80% or more to be complete. The text of the revised RCD now states (p. 2):
>
> "A study in which human volunteers were exposed by inhalation for 6 hours to 1 ppm *cis/trans* 1,3-D showed that respiratory uptake was ~80% for both isomers. Initial phase half-lives for urinary excretion of *cis* and *trans* N-acetyl cysteines (major conjugation products of 1,3-D) were 4.2 and 3.2 hours, respectively. Terminal phase half-lives were 12.3 and 17.1 hours. This study showed rapid and near-complete (~80%) uptake through the lung and subsequent metabolism to excretable compounds in humans."

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Oncogenicity

Draft RCD
Page 5/Paragraph 3: "In view of the apparent dose dependence and the evidence for genotoxicity…"

DAS Comments:
1,3-D is not genotoxic. The evidence cited by DPR is based on old formulations and flawed studies and ignores the most recent and relevant studies. This is explained in further detail in these comments.

> **DPR-HHAB response:** An new appendix has been added to the revised RCD which substantiates why 1,3-D should be viewed as genotoxic. Further details are provided below in our answers to the relevant DAS comments.

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Draft RCD
Page 5/Paragraph 3: "Application of the appropriate RGDR scalar to the dose levels used in the 2-year study, followed by BMC modeling of the incidence rates, generated AUCs (Air Unit Concentration) of 0.018 ppm^{-1} and 0.0059 ppm^{-1} for non-occupational and occupational exposure scenarios, respectively."

DAS Comments:
It would be helpful to cite EPA IRIS' (EPA 2000; http://www.epa.gov/iris/subst/0224.htm) derivation of cancer potency (air unit risk). Also, the equivalent (mg/kg/day)$^{-1}$ potency, i.e., 0.014, should be presented since (mg/kg/day)$^{-1}$ potency is used in CDPR's lifetime average daily dose modeling and lifetime excess cancer risk estimation. Derivation of the value of 0.014 (mg/kg/day)$^{-1}$ should also be provided

> **DPR-HHAB response:** We did not deem it necessary to cite EPA IRIS's air unit risk derivation, as our calculation is expressed fully in the RCD. However, the equivalent (mg/kg/day)$^{-1}$ portal of entry potency of 0.014 used to calculate ambient lifetime risk is derived fully in Appendix VIII (p. 273) of the revised RCD. A simplified version of that

calculation is provided here, along with the potency arrived at when assuming a systemic mode of action:

Portal of entry mode of action
$0.018 \ (ppm)^{-1} = 0.004 \ (mg/m^3)^{-1}$ *i.e.,* using the 1,3-D conversion 1 ppm = 4.54 mg/m^3
$0.004 \ (mg/m^3)^{-1} \div 0.28 \ m^3/kg = \textbf{0.014 (mg/kg)}^{\textbf{-1}}$

Systemic mode of action
$0.062 \ (ppm)^{-1} = 0.0137 \ (mg/m^3)^{-1}$ using the 1,3-D conversion 1 ppm = 4.54 mg/m^3
$0.0137 \ (mg/m^3)^{-1} \div 0.28 \ m^3/kg = \textbf{0.049 (mg/kg)}^{\textbf{-1}}$

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Reproductive and developmental toxicity

Draft RCD
Page 5/Paragraph 4: There was little indication from the reproductive and developmental inhalation toxicity studies that 1,3-D poses a health risk to humans with respect to these parameters.

DAS Comments:
Dow AgroSciences concurs with DPR's assessment of the lack of reproductive and developmental toxicity from 1,3-D. Further, as explained in greater detail later, these studies provide supporting evidence that there are no age-related effects from 1,3-D and addition of age-related uncertainty factors is not necessary.

> **DPR-HHAB response:** The apparent lack of reproductive or developmental toxicity led us to use an additional 3x database factor, which we considered to be necessary in order to protect potentially vulnerable young human populations. To our knowledge, there are no available studies in which young animals were exposed by the inhalation route.

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Exposure estimation

Draft RCD
Page 5/last paragraph: The term "handwand injection" is used to characterize the device for applying 1,3-D in holes prior to planting trees or vines.

DAS Comments:
The correct term used in product labels is "handheld equipment". Typically, "handwand" is used as a description of a hand-held spraying device. 1,3-D is not sprayed, but rather injected a minimum of 18" into the soil using an "application wand" such as an "injection auger", rodding device or soil probe.

Regardless of terminology, these are spot applications only used for individual tree replants, not for orchard-wide applications. It would be cost prohibitive to treat significant acreage in this manner. Thus this section greatly overestimates applicator exposures from this application method.

> **DPR-HHAB response:** "Hand-wand" was changed to "injection auger" in the revised RCD. Some of the exposure estimates for this scenario were revised based upon the AGRIAN database. The short-term air concentration (STAC) value was not altered. It is possible for a worker to apply 1,3-D using the injection auger for the assumed daily work period of 8 hours. Moreover, a maximum application rate is not specified for this method on either the product labels or CA permit conditions. Hence, the rate in pounds of AI/acre had to be estimated from the number of sites (tree-holes) an applicator could potentially treat in an 8-hr workday. As described in the EAD, this estimate and the exposure estimates were generated using surrogate data from a chloropicrin study due to a lack of 1,3-D empirical data. In the latest version of the RCD, the long-term exposure estimates (seasonal, annual, and lifetime air concentrations), were eliminated based on a lack of use data for the injection auger method in the AGRIAN PUR database.
>
> As stated in the revised RCD, two databases are available for investigating use of 1,3-D. The first is the Pesticide Use Report (PUR) database maintained by DPR, while the other is the AGRIAN® PUR database generated by Dow AgroSciences. California requires reporting of all agricultural applications of pesticides, as well as other uses when pesticides are applied by a licensed applicator. These data are collected in DPR's Pesticide Use Report (PUR) database. The AGRIAN® PUR records are specific to 1,3-D and are part of the California Management Plan which helps ensure that the amounts of

1,3-D applied in California do not exceed the use limits set by DPR (CDPR, 2002a). The pesticide use records in the AGRIAN® database contain much more information specific to 1,3-D (e.g., specific method of application, application date, application company, application rate), than that provided in DPR's PUR database and are more up to date. Moreover, the records for the total pounds applied statewide for the latest 4 years in the DPR PUR database (2010-2013) are within 2.1 to 6.4% of the totals for these years on the AGRIAN® PUR database (Table I).

Table I. Pounds of 1,3-D applied: Comparison of annual statewide totals between the DPR and AGRIAN PUR databases

Year	DPR PUR database	AGRIAN® PUR database	% Difference
2010	8771323	8953350	2.1
2011	10907012	11197043	2.7
2012	12012976	11248926	6.4
2013	12917296	13216014	2.3
2014	no data	13775265	n/a

As a result, the bulk of the use seasons and the estimated seasonal application rates used for estimating exposure in this document were derived from the latest 5 years (2010-14) of use records in the AGRIAN® PUR database (DAS, 2011; DAS, 2012; DAS, 2013; DAS, 2014; DAS, 2015). The use of the AGRIAN PUR database allowed for additional occupational exposure scenarios (e.g., deep shank) and method-specific use seasons (e.g., shallow shank, deep shank, and drip).

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Draft RCD
Page 8 / Summary Table I

DAS Comments:
The title for Summary Table I is missing. Additionally the footnotes *a* and *b* are missing. To inform readers and risk managers as to the likelihood of occurrence, the percentiles associated with 30, 50 and 70 year residency durations should be footnoted. The percentiles can be based on the DAS residency/mobility survey as discussed in the RCD, or other survey data sources (see ARB 2015, OEHHA 2015, EPA Exposure Factors Handbook 2011).

       DPR-HHAB response: We have revised the RCD to reflect the suggested changes.

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Risk analysis

Draft RCD
Page 9/Paragraph 1: "For children, who are presumably exposed only under non-occupational scenarios, the target MOEs was 100. The extra ~3-fold factor was due to database uncertainty arising because no toxicity studies were conducted on young animals. Consequently, we had no way of assessing the possibility that infants and children might be more susceptible to the toxic effects of 1,3-D. In addition, the lack of default surface area values for infants and children precluded RGDR-based calculations for those demographics."

DAS Comments:
This statement is incorrect. Toxicology data involving exposure to young animals does exist. Toxicity data of 1,3-D in mammals covering stages prior to conception, prenatal, postnatal, and post-weaning periods was provided in two developmental toxicity studies in rats and rabbits and one two-generation reproduction study in rats. These studies were conducted via the inhalation route and are thus, relevant to human exposure comparisons. In these studies, comprehensive examinations of fetuses or young animals including body weight, gross pathology, histopathology, external alterations provide no evidence of increased susceptibility following exposure to 1,3-D. This statement is clearly supported by the quantitative comparison of maternal and developmental/reproductive/offspring NOAELs/LOAELs (See Table below).

Summary of Developmental and Reproductive NOAELs / LOAELs					
		Maternal/Paternal (ppm)		Developmental/Reproductive/offspring (ppm)	
Study	Doses (ppm)	NOAEL	LOAEL	NOAEL	LOAEL
Developmental study in rats	0, 20, 60, 120	<20	20	60	120
Developmental study in rabbits	0, 20, 60, 120	20	60	120	NA
2-generation reproductive study in rats	0, 10, 30, 90	30	90	90	NA

NA: not applicable

As recognized by the U.S. EPA, the FQPA safety factor can be reduced to 1X and no additional safety factors are needed. The EPA risk assessment for 1,3-D stated that

> "*Based on the hazard and exposure data, the 1,3-dichloropropene risk assessment team has recommended that the FQPA Safety Factor be reduced to 1X. There is a complete toxicity database for 1,3-dichloropropene and exposure data are complete or are estimated based on data that reasonably account for potential exposures. There is no evidence of susceptibility following in utero and/or postnatal exposure in the developmental inhalation toxicity studies in rats or rabbits, and in the 2-generation inhalation rat reproduction study. There are no residual uncertainties concerning pre- and post-natal toxicity and no neurotoxicity concerns. The chronic and cancer dietary food exposure assessments assume 100% crop treated for grapes, the commodity of interest. The drinking water exposure assessment is based on conservative models and monitoring data. The residential exposure assessment is not likely to underestimate bystander exposure. Based on these data and conclusions, the FQPA Safety Factor can be reduced to 1X.*"

Based on robust and complete toxicity data, the extra ~3-fold factor is not appropriate and should be reduced to 1X. Subsequently, for children, under non-occupational scenarios, the target MOEs of 30, the same as adults, should be applied. Both DPR and the EPA have reviewed acceptable

prenatal developmental toxicity studies in rats and rabbits and an acceptable two-generation reproduction study in rats following inhalation exposures.

DAS respectfully requests reconsideration of this statement in light of the available data, harmonization with federal standards, and to revise the RCD accordingly.

> **DPR-HHAB response:** Our concern is that there are no studies in which young animals were directly exposed to 1,3-D by inhalation. In the developmental studies (John *et al.*, 1983; Kloes *et al.*, 1983), only the (pregnant) mothers were directly exposed. Offspring only received indirect exposure through maternal respiratory intake. In the 2-generation reproduction study, mothers were separated from their newborns before placement in the respiratory chambers (Breslin *et al.*, 1987). Exposure of F1b animals did not start until they were 5-7 weeks of age. Due to lack of default RGDR factors for young animals and young humans (particularly surface areas and minute volumes), we could not estimate at this time infant / child-specific endpoints for the inhalation route. Consequently, we imposed the 3x factor, which we referred to as a database factor due to the lack of the relevant studies. We chose an uncertainty factor of 3 rather than 10 in view of the apparent mildness of the acute, subchronic, and chronic endpoints.

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Draft RCD
Page 9/Paragraph 4 "sank"

DAS Comments: Typographic error: "sank" should be "shank".

> **DPR-HHAB response:** Corrected.

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Draft RCD
Page 10/Paragraph 5: "All of the resident / bystander and ambient scenarios (annual) showed oncogenic risk values that were above the negligible oncogenic risk standard of $1x10^{-6}$."

DAS Comments:
It is unclear how CDPR distinguishes a "target" MOE from a "risk standard". DPR has allowed registration of materials with oncogenic risk of $>10^{-5}$ in the past such as permethrin and

propoxur, so it would seem that oncogenic risk is also relative to a target. For example, USEPA's Non-Dietary Cancer Policy (USEPA 1996) recommends that the target for workers is somewhere between 10^{-4} and 10^{-6}, and for residents between 10^{-5} and 10^{-6}.

> **DPR-HHAB response:** In general, DPR-HHAB risk assessments adhere to the negligible risk standard of 10^{-6} established by USEPA (USEPA, 1996). While exceptions may be made for individual chemicals depending on circumstances involving the quality of data or the status of the impacted populations (decisions which may fall to the risk management process), this standard is maintained in the present risk assessment.
>
> The policy as stated in the USEPA memo is as follows:
>
> "OPP will continue to apply its existing policy to consider dietary and non-dietary risks of 10^{-6} and less to be negligible, and thus it would not typically pursue risk reduction measures for such negligible risks. OPP will not allow dietary risks to exceed 10^{-6}; or non-dietary risks to exceed 10^{-4}, except in those cases where it has determined that benefits exceed the risks. OPP will examine non-dietary risks in the 10^{-5} to 10^{-4} range to determine whether the benefits of use outweigh the risks and will seek ways to mitigate unacceptable risks. This policy allows for the consideration of a wide range of factors in making a risk management decision for non-dietary risks. These factors may include: risk to individuals, number of people exposed, weight of scientific evidence regarding carcinogenicity, lower risk alternatives, and benefits associated with the pesticide under review. In general, OPP will tolerate less risk to individuals as the size of the exposed population increases. Therefore, for the largest exposed populations, including residents and agricultural workers, OPP will seek to reduce the individual risks to the greatest extent feasible, preferably to 10^{-6} or less. The goal is to ensure that there is a minimum level of protection from exposure to pesticides for workers, residents, bystanders and vulnerable populations, particularly children. OPP will strive to ensure that this policy is consistently applied to all, pesticide program decisions."

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Draft RCD
Page 13/Summary Table III

DAS Comments:
Air concentration values for three mobility scenarios are presented in Table I for HEE5CB (high, intermediate and low mobility) but only two exposure scenarios are presented in Table III (page 13). Were all three scenarios evaluated but only two reported?

Non-occupational scenarios: The last two scenarios (HEE5CB) are both described as "high mobility". Is one of these low or intermediate?

> **DPR-HHAB response:** All mobility scenarios have been included in the revised RCD.

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Risk appraisal – toxicology

Draft RCD
Page 14/second to last bullet: "With the exception of genotoxicity, the possible effects of metabolites, degradates and impurities in the toxicity studies were not evaluated in this assessment."

DAS Comments:
This is an incomplete summary of the risk appraisal and does not reflect that each toxicology study takes into account the effects of metabolites, degradates and impurities. Referring to impurities in the commercial form of 1,3-D; studies with epichlorohydrin are not relevant, because the animals are being dosed with technical active ingredient that includes degradates and impurities, and conversion to metabolites occurs in every test species including humans.

> **DPR-HHAB response:** While 1,3-D degradates and impurities may be present in all toxicity studies, we do not know the levels of these compounds in any particular study, particularly as they may change with storage and handling. In addition, the presence of active metabolites changes from individual to individual depending on their metabolic status. For these reasons, we consider metabolites, degradates, and impurities to contribute to the inherent uncertainties in the interpretation of the toxicity studies examined for this assessment.

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Exposure appraisal

Draft RCD
(No page / paragraph number indicated):   Surrogate data from chloropicrin exposure studies…

DAS comments:
Some of these exposure scenarios are unrealistically over estimated as explained in greater detail later. For example, tarp removers are required to wear respirators according to recent label amendments. Although some labels such as Tri-Cal Trilone II are still pending approval at USEPA, those labels are for products not currently in production. Also, applicator (hand-wand) is an infrequent method that is a spot treatment, not used on large acreage or for extended periods of time.

> **DPR-HHAB response:** Five of the labels for active products on the DPR product label database for 1,3-D allow for exposures without respiratory protection (Telone II, Pic-Clor 60 EC, Trilone II, Telone EC, and Inline). For all five of these product labels, a half-face respirator is required for the handler (*e.g*., tarp remover) entering the treated area for 1-5 days following application. However, for three of these product labels (Telone II, Tri-Cal Trilone II, and Telone EC), there is no information on respirator requirements for handlers entering the treated area after the 5-day fumigation period. The other two labels (Pic-Clor 60 EC and Inline) state that the handler entering the treated area 5 days or more after the application doesn't have to don respiratory protection unless irritation of the eyes and nose occurs. Moreover, the chloropicrin tarp remover breathing-zone air monitoring data used to derive the 1,3-D air concentrations was collected 7 days post-application. Due to these issues and the fact that CA permit conditions for 1,3-D do not address this particular scenario, a respiratory protection factor for the half-face respirator was not incorporated into the exposure estimate calculations.
>
> For the response to the comment concerning the applicator using the hand-wand, please see the response to the DAS comment on the draft RCD, page 5/last paragraph, on page 6 of this memorandum.

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Draft RCD

Page 15/last paragraph: "Both MCABLE and HEE5CB…may have been underestimated in some cases." "However, …may have alleviated the potential impact of the air concentration underestimation, therefore provide a better reflection of the range of exposures and oncogenic risks associated with the use of 1,3-D."

DAS Comments:

MCABLE and HEE5CB models actually provide conservative estimates for risk assessment. SOFEA2 has been validated against 14½ months of continuous 1,3-D measurements at made 9 locations in Merced. Based on DPR review comments outlined in the memorandum from Terri Barry (Aug 12, 2015), the Merced weather data collected during the monitoring study was corrected to address the stability class and mixing height issues identified by DPR and DAS. As a result of these corrections to the weather data, SOFEA2 comes closer to predicting the highest concentration observed at receptor #5 in the Merced monitoring study (see more detailed discussion below) than it did using the original weather data, and when the receptor density is increased, the maximum modeled concentrations exceed the maximum measured concentration. In any case, the MHs in the original weather file had been 'calibrated' so that the model predicted a global annual average concentration that matched the measured annual average concentration. The mixing height and stability class corrections result in improved variability of modeled 1,3-D concentrations that more closely matches the variability of the measured 1,3-D concentration distribution. The annual average concentrations simulated for the purpose of risk assessment in Merced and Ventura contain many concentrations that exceed what has ever been observed in any of the numerous 1,3-D ambient monitoring studies, and therefore the model simulated 1,3-D concentration distributions are considered conservative estimates for risk assessment via either the MCABLE or HEE5CB model.

> **DPR-HHAB response:** As stated in the draft RCD (page 163), we have identified additional issues with SOFEA-2 including an erroneous mixing-height correction and atmospheric stability class designation (Barry, 2015). We understand that DAS is addressing these issues of SOFEA-2. Hence, we will reevaluate the performance of SOFEA-2 when the revised model is available.

II.   INTRODUCTION

A.   CHEMICAL IDENTIFICATION

Draft RCD
Page 16/Paragraph 3: "While the mechanism of pesticidal action is unclear, 1,3-D may work by inactivating vital enzymes through sulfhydryl or hydroxyl binding."

DAS Comments:
The "binding" is actually formation of covalent bonds due to nucleophilic displacement.

> **DPR-HHAB response:** Agreed. The wording is amended in the revised RCD to reflect this point (p.18).

B. REGULATORY HISTORY AND CURRENT REGULATORY LIMITS

Draft RCD
Page 19/Paragraph 1: "On April 9, 2001 DPR issued a Risk Management Directive on "Managing 1,3-Dichloropropene (Telone) Chronic Risks" (Gosselin, 2001). This directive set the acceptable oncogenic lifetime (70 year) risk at 1×10^{-5} at the 95th percentile for 1,3-D."

DAS Comments:
It is important to note that the determination by CDPR to use an oncogenic lifetime risk at 1×10^{-5} was due to the layers of compounding conservativism in the risk assessment, including the use of the 95th percentile exposure. Now that DPR is using 10^{-6} as a risk target, maintaining the use of the 95th percentile exposure is excessively conservative and departs from generally accepted practice of using the arithmetic mean when calculating at 1×10^{-6}. By compounding both the 95th percentile exposure estimate with use of a 95th percentile upper confidence limit potency factor the resulting risk estimate is now at the 99.75^{th} percentile.

> **DPR-HHAB response:** We have revised the lifetime cancer risk calculations based on lifetime average daily dose (i.e., mean value) and a 95th percentile upper confidence cancer potency factor. Please see response to the final comment on page 10 of this memorandum for addressing the issue of target cancer risk value.

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C. PRODUCT FORMULATIONS AND USES

Draft RCD
Page 21/Table II.2: This table lists the % chloropicrin in products used in CA.

DAS Comments:
While the listed products may be registered, many are not actually in use. It might be instructive to denote which products are actually being commercialized. This can be determined by the availability of product specimen labels on the AGRIAN, Inc. on-line database, http://www.agrian.com/labelcenter/results.cfm.

> **DPR-HHAB response:** Per the DPR PUR database, there were six 1,3-D products used in California between 2009 and 2013: Pic-Clor 60, Pic-Clor 60 EC, Telone II, Telone C-35, Telone EC, and InLine. The AGRIAN database provided by DAS (http://www.agrian.com/labelcenter/results.cfm) contains three additional 1,3-D products registered in California: Telone C-17, TriForm 80 and TriForm 80EC. Every pesticide product with active registration can be used in the State of California. As of August of 2015, there are 17 such products, now listed in Table II.2 of the revised RCD.

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1. Pesticide Usage

Draft RCD
Page 26/Figure II.2: Seasonal applications by county and month

DAS Comments:
These data are subsequently used to estimate annual and chronic exposure with the assumption that any use greater than 5% of the total can produce seasonal exposure. One problem with this assumption is that a resident does not live all over Fresno County, for example. Additionally, crops and cropping practices vary from North to South and East to West within the same county. Detailed use reports from AGRIAN can be used to refine annual and chronic exposures down to the level of Township, Section:Range, and even by company by date.

> **DPR-HHAB response:** Our use of PUR data and the 5% of annual use assumption are consistent with other RCDs in which annual use patterns are based on the assumption that individuals are less likely to be exposed to a particular pesticide during intervals of low use. Like the AGRIAN database, the PUR database allows use to be summarized at the township, range, and section level, as well as at the county level. However, the approach we use of averaging across 5 years to minimize the likelihood that the annual pattern would reflect an anomalous year also leads to greater weight being placed on each application when small numbers of applications are considered. With small numbers of applications, as would occur in smaller use areas, the estimated high-use season often expands if applications occur at slightly different times each year. Additionally, individuals can live in one part of a county and work in another or otherwise move about. There are also uncertainties inherent in using past application patterns to represent the future. For these reasons it does not make sense to overly refine our estimates.
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> These data were not used for estimating the annual and lifetime residential exposures in the revised RCD. This document assesses the risk of 1,3-D use in specific counties, townships/sections, and statewide.

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D. CHEMICAL DESCRIPTION AND PHYSICO-CHEMICAL PROPERTIES

Draft RCD
Page 27/Table II.6 lists color as "white or amber".
"Formulations consist of approximately equal parts of the "Z" (*cis*) and "C" (*trans*) isomers."

DAS Comments:
Clear or colorless is a more appropriate descriptor than "white".
The statement/ entry should be corrected so that it reads: "Formulations consist of approximately equal parts of the "Z" (*cis*) and "E" (*trans*) isomers." i.e., "E" not "C".

> **DPR-HHAB response:** These errors were inadvertently left in the revised RCD. They will be noted in a future "Errata" document.

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III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Draft RCD
Page 29/Paragraph 2: "Blood concentrations averaged about 0.7 ng/g for *cis* and about 1.3 ng/g for *trans* Telone, respectively, for most samplings during the exposure period."

DAS Comments:
These concentrations provide some perspective on tissue concentrations in humans exposed at 1 ppm, and a basis for comparison to concentrations used in the *in vitro* genotoxicity studies.

> **DPR-HHAB response:** No response necessary.

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Draft RCD
Page 29/Paragraph 4: "About 44% of the mass of those conjugates was attributable to parent Telone. Thus although the NAC conjugates constituted large portions of absorbed Telone II, particularly for the *cis* isomer, fate of much of absorbed Telone II was not addressed in this study."

DAS Comments:
This study demonstrates that humans have uptake almost identical (~80%) to rodents following inhalation dosing. The study also indicates that humans excrete the same metabolite as rodents that accounts for ~44% of the inhaled dose, and that metabolite results from conjugation of 1,3-D with glutathione as in rodents.

> **DPR-HHAB response:** While the 80% inhalation uptake in the human study shows that humans and rodents are similar in this regard, there is a considerable fraction of the inhaled dose that is not conjugated by glutathione, as stated in the revised RCD (page 34): "although the 1,3-D NAC conjugates constituted large portions of absorbed Telone II, particularly for the *cis* isomer, fate of much of absorbed Telone II was not addressed in this study." This leaves an unknown portion of the administered dose unaccounted for in humans.

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B.   ACUTE TOXICITY

1. Illness reports in humans

DAS Comments:
DPR's analysis of illness reports over the past 30 plus years confirms the low risk of acute exposures to 1,3-D, especially considering the amount of use in California during that time period. It would be helpful to put the number of alleged illness and injury reports into context with respect to the number of applications during those years. **Less than 0.1% of applications in the past 10 years resulted in a report of alleged injury or illness.** This important context should be included in the Risk Characterization Document.

> **DPR-HHAB response:** An attempt to compare numbers of applications to numbers of illness episodes is confounded by the fact that illnesses are not comprehensively reported, nor is the true rate of underreporting known (Mehler *et al.*, 2006; Osorio, 2007). Illness reports are not comprehensive because not all affected individuals relate their symptoms to pesticide exposure, some experience limited access to medical care or have care that occurs away from the work zone, and treating physicians may not recognize effects related to pesticide exposure. Also, illness reports are almost exclusively limited to acute exposures and symptoms, and thus no statements about lack of chronic health impacts can be supported by the illness data. As such, no changes have been made to the RCD in this regard.

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Draft RCD
Page 33/Paragraph 4: "In California between 1982 and 1990, 51 cases were reported to the California Department of Pesticide Regulation's Pesticide Illness Surveillance Program (PISP)… Of these 51 cases, the health effects attributed to exposure to 1,3-D alone, or in combination with other pesticides, were rated as definite (33 cases), probable (9 cases) or possible (9 cases). The health effects involved were systemic (16 cases), eye (14), skin (18), and combined eye-skin effects (3)."

DAS Comments:
It would be helpful for DPR to put the number of alleged illness into perspective relative to the number of applications made. From 1989 to 1990, approximately 7,890 applications were

recorded (CDPR's Pesticide Use Reporting database only provides data beginning in 1989). Even when using only 2 years of use data compared with the 9 years of incident reporting, only 0.5% of all applications were implicated in either a definite or probable illness incident. Since this is only based on 2 years of use reporting instead of 9, the actual percent illness reports is even lower. It is also unclear from the report if these were attributed to 1,3-D alone or to combination products.

DPR-HHAB response: See response to previous comment.

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Draft RCD
Page 33/last paragraph: "Then, in the 10 years from 2002 to 2011, the PISP identified 17 exposure episodes that gave rise to 71 cases associated with 1,3-D either alone or in combination with chloropicrin (Figure III.2)(CDPR, 2015a). The 71 cases were classified as 1 definite, 54 probable and 16 possible."

DAS Comments:
It would be helpful for DPR to put the amount used and coincident exposures into perspective (See table in Appendix A). From 2002-2011, over 20,004 applications of 1,3-D were made. **Thus the 17 exposure episodes represent less than 0.1% of all applications.** This context would be useful to include in the Risk Assessment document. Further, it would be more appropriate to only include "definite" and "probable" cases. "Possible" cases lack sufficient evidence to attribute them to 1,3-D exposures. In addition, all but two were episodes involving chloropicrin. The symptoms described, "watery and burning eyes" are indicative of chloropicrin exposure. Thus only 2 episodes out of a total of over 20,000 applications were definitively or probably attributed to 1,3-D applications alone.

DPR-HHAB response: Reported illnesses associated with 1,3-D are summarized consistent with DPR practice and classified as definite, probable, or possible. The respective numbers of illnesses in each category and definitions of the three terms are given to allow readers to weigh their significance. The revised RCD (page 42) also states that symptoms reported in most cases are consistent with exposure to chloropicrin.

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Draft RCD
Page 34/Paragraph 2: "Two scenarios contributed to the majority of documented cases. Of the 71 cases, 64 (from 10 episodes) were due to bystander exposure, where people adjacent to recently-treated fields experienced symptoms. Six cases were due to flushing tractor lines or repairing hoses/drip lines."

DAS Comments:
One of the examples of bystander exposure is especially noteworthy, because it occurred in a residential neighborhood that objected to the fumigation and tried to prevent it from happening. It is not surprising that seven of the neighbors subsequently complained of illness following application even though, per the CAL PIQ database, "*The CAC, DPR and observers identified no violations of regulations or permit conditions*" and "*Repeated readings at the edge of each field indicated no measurable amounts of the fumigants escaped from the fields*." The database only assigned a "possible" relationship to the episode, indicating there was insufficient evidence to link the application to the complaints.

     DPR-HHAB response: See response to the previous three comments.

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Draft RCD
Page 34/Paragraph 3: "Of the 72 recently reported cases (*i.e.*, between 1998 and 2011), there were 5 cases with 1,3-D used alone between 1998 and 2011.

DAS Comments:
Clarification is needed to explain that "there were 5 cases *from 3 episodes* with 1,3-D used alone between 1998 and 2011." Further, only one of those episodes was a "probable" relationship to 1,3-D exposure, the other two were unconfirmed "possible" relationships, and only one of those was related to alleged "drift" to workers in an adjacent field. Having only 1 "possible" drift incident due to 1,3-D alone, out of over 20,000 applications over the course of over 10 years is compelling evidence that use of 1,3-D is associated with a very low concern for human illness accruing from exposure and acute toxicity. It is also strong validation of the effectiveness of DAS's product stewardship commitment and our business strategy.

     DPR-HHAB response: See response to comment above.

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Draft RCD
Page 34/last paragraph: The remaining 67 cases involved both 1,3-D and chloropicrin…Most of the cases involving 1,3-D and chloropicrin show dominance of eye effects, suggesting that the reported eye symptoms may be due to the chloropicrin.

DAS Comments: This is a crucial factor in evaluating illness attributable to 1,3-D. We concur that given the dominance of eye effects such as burning and watery eyes, the causative agent is more likely to be due to chloropicrin than 1,3-D. Recent regulatory changes (e.g. buffer zones) and improvements in tarp permeability should further reduce incidents of alleged exposure to both soil fumigants.

      DPR-HHAB response: See response to comment above.

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Draft RCD
Page 35/Table III. "Eye, Respiratory & Systemic" row.

DAS Comments:
There is a typo on the "Eye, Respiratory & Systemic" row which reads 1 in the total column and should be 11.

      DPR-HHAB response: This error was inadvertently left in the revised RCD. It will be noted in a future "Errata" document.

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C.   SUBCHRONIC TOXICITY

Draft RCD
Page 41/Table III.3.b: Nasal epithelial hyperplasia and degeneration of olfactory epithelium are listed as effects.

DAS Comments:
As noted in the Executive Summary, nasal epithelial hyperplasia appears to be an indicator of exposure, but it is reversible and is an equivocal adverse effect. Nasal hyperplasia has a long tradition of use as a regulatory endpoint and has been applied to many different types of

chemistry. However, as noted in Appendix C, nasal hyperplasia is an effect observed transiently in rats i.e., very slight hyperplasia was evident at 13 weeks, but at 26 and 52 weeks, nasal hyperplasia was not observed. Thus, DAS proposes that the same effect observed in mice would be a better, yet still extremely conservative subchronic endpoint. Nasal epithelial hyperplasia does occur in humans, and over half of the children in the US live in areas that exceed the ozone levels associated with epithelial injury (Carey et al., 2011).

> **DPR-HHAB response:** While nasal epithelial hyperplasia is an indicator of exposure, it does not negate the possibility that the hyperplasia may also result from cellular or tissue damage, or that it is an undesirable outcome. Reversibility in rats – as opposed to stability in mice – is not a sufficient argument against that possibility. Thus we consider the subchronic histopathologic observations in rats to reflect an adverse effect.

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D.   CHRONIC TOXICITYAND ONCOGENICITY

Draft RCD
Page 47/last paragraph: "A chronic NOEL of 5 ppm was determined based on the single 20-ppm male with nasal epithelial histopathology."

DAS Comments:
Both the effect (erosion of the olfactory epithelium) and statistical insignificance (1 of 50 animals exhibiting this sign) make this a highly suspect toxicologic endpoint for regulation.

> **DPR-HHAB response:** Nasal epithelial hyperplasia at 20 ppm in the rat, regardless of its low incidence, is likely the result of 1,3-D exposure and cannot be ignored. Even so, this study was not designated as critical, largely because of the low incidence rate.

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Draft RCD
Page 52/last paragraph: "It seemed likely that the stomach histopathology described here resulted from movement of inspired Telone from the respiratory tract into the stomach."

DAS Comments:
This statement is difficult to justify. While it is interesting speculation, the authors provide no credible suggestion for how the 1,3-D got to the stomach.

> **DPR-HHAB response:** This comment was intended only to provide a plausible scenario for the observed stomach histopathology. Absorption through the respiratory tract and subsequent redistribution to the stomach through the circulatory system was considered to be less likely.

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Draft RCD
Page 53/last paragraph: "The co-occurrence of respiratory epithelial hyperplasia / hypertrophy and bronchioloalveolar adenomas suggested that they were induced by 1,3-D as part of the same or similar process."

DAS Comments:
This statement is difficult to justify. The effects were not observed in the same region of the respiratory tract, i.e., one is in the nasal turbinates, and the other is in the lung. The hyperplasia was found early on (i.e., readily apparent after 90 d) with no indication of intensification or progression of effect with time, while the adenomas only occurred in elderly animals (i.e., they were not observed at the 1 year interim sacrifice). Perhaps more importantly, the exposure to either resident bystanders or workers is intermittent and seasonal (a few months per year) in nature, and it is extremely doubtful that a reversible effect such as nasal hyperplasia can result from intermittent, seasonal exposure.

> **DPR-HHAB response:** We consider it not coincidental that a damage response in the upper respiratory tract is in some way related to the tumor response in the lower tract. The absence of tumors in the upper tract is likely due to the fact that there are far fewer cells in that area. On the other hand, the apparent absence of frank hyperplasia in the lower tract may be a function of lower concentrations of 1,3-D that reach those areas. Nonetheless, sub-rosa (*i.e.*, undetected) irritation in the lower tract could still be present.

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E.   GENOTOXICITY

Draft RCD

Page 62/last paragraph: "Altogether, these studies, provide convincing evidence that 1,3-D, along with its oxidative metabolites and autoxidation products, has genotoxic potential."

DAS Comments:

There are numerous concerns associated with DPR's analysis of the genotoxicity data. First, DPR seems to be giving equal credence to GLP and non-GLP studies. Non-GLP studies where the original data cannot be produced should not be considered as reliable or credible as GLP studies where all of the data is required to be provided. Similarly in some studies, the concentrations required to produce the effects *in vitro* cannot be achieved *in vivo* from inhalation, casting doubt on those non-physiologic results. When the non-physiologic doses are included in a non-predictive study design conducted in a non-GLP laboratory, they should not carry the same weight of evidence as more robust studies.

There is an extensive body of literature on the *in vitro* and *in vivo* genotoxicity of 1,3-D. Results from most, if not all of the early studies on genotoxicity were confounded by the use of low purity and/or uncharacterized test material, often containing the known genotoxic stabilizing agent epichlorohydrin. In addition, several of the *in vitro* studies were confounded when researchers attempting to purify 1,3-D in the laboratory often generated mutagenic artifacts during the process that invalidate their findings.

Nonetheless, some *in vitro* assays did identify a relatively restricted *in vitro* genotoxic activity for 1,3-D but they are considered not relevant to *in vivo* situations or the very low human occupational or ambient environmental exposure levels. Of particular interest in this context is the protective role – which has been demonstrated experimentally – provided by the addition of normal physiological levels of glutathione (GSH) to these *in vitro* systems. In effect, the GSH reduces the genotoxic response observed in some of these *in vitro* assays and calls into question the relevance of even the positive *in vitro* findings for *in vivo* risk assessment.

There are several studies examining the *in vivo* genotoxic potential of 1,3-D. Dr. Errol Zeiger, an internationally renowned genetic toxicologist, provided an independent expert opinion on the weight of evidence for the *in vivo* genotoxicity of 1,3-D (Zeiger, 2005) and concluded that the genetic damage induced by 1,3-D in rats and mice was limited to only non-specific DNA strand breakage which was not the result of direct DNA interaction. This expert opinion report has been

submitted to DPR. The salient findings of the *in vivo* studies are listed below and provided in more detail in Appendix B:

- Mouse micronucleus assay – negative findings in test guideline-quality studies employing test material lacking a genotoxic stabilizer.
- Big Blue[TM] mouse *in vivo* mutagenesis model – negative findings in tumor target tissues (lung and liver).
- ^{32}P-Postlabelling assay – negative findings for DNA adducts in both rat liver and mouse lung, target tissues for tumors in these species, following inhalation exposure.
- Dominant lethal assay in rat germ cells – negative findings in test guideline-quality study.
- The *in vivo* studies that were positive – induction of micronuclei or chromosome aberrations – are compromised by the presence of 1% epichlorohydrin (Shelby *et al.*, 1993) or had an inadequate study design (i.e., single animal in vehicle control group (Kevekordes *et al.*, 1996).
- Several DNA fragmentation assays have been conducted at relatively high dosages with "positive" findings. These studies suffer from basic methodological problems related to generation of artifacts secondary to cytotoxicity, lack of information about epoxide stabilizer in the test material, and general inconsistency between studies.

The genotoxic potential for 1,3-D has been adequately investigated. The salient question is not whether 1,3-D (or any chemical) can have some intrinsic genotoxic potential in artificial test systems at exposure concentrations well above the physiologically relevant range. Under such circumstance, it has been well demonstrated that many chemicals commonly assumed to be benign including table salt, sugar and juices from *Brassica* vegetables would be considered genotoxic (Pottenger *et al.*, 2007). Rather, only the most relevant data-set, typically well conducted *in vivo* studies, for characterizing human risk should be used in making the assessment. For 1,3-D such studies show a consistent lack of genotoxic potential attributable to the action of antioxidant defense mechanisms.

> **DPR-HHAB response:** The revised RCD now has two appendices (VI and VII) addressing the genotoxicity of 1,3-D in greater detail. As explained in Appendix VI, 1,3-D and/or its metabolites can induce (1) gene mutation in the Ames test and the mouse lymphoma TK assay; (2) sex-linked recessive lethals in *Drosophila*; and, (3) sister-chromatid exchanges in CHO cells. Importantly, none of these positive findings are negated by the postulated presence of 1% epichlorohydrin in the 1,3-D test material based on the following:

- In the Ames test using TA100 without S-9 (Eder *et al.*, 2006), mutagenicity still was seen with 1,3-D test materials after their being highly purified using silica-gel. In testing with S-9, the mutagenicity of 1,3-D increased with amount of S-9 used (*trans* isomer only) and the duration of the preincubation time (both isomers) (Neudecker and Henschler, 1986). By contrast, the use of S-9 reduced the mutagenic response of epichlorohydrin towards TA100 (Eder *et al.*, 1980).

- With the mouse lymphoma TK assay (without S-9) (Myhr and Caspary, 1991), mutagenicity was observed both times in testing 10 nL of 1,3-D/mL of culture medium: the average mutation frequency was increased by factors of 12 and 8 relative to the respective vehicle (ethanol) controls (p. 75 of that study). If indeed 1% of that 10 nL/mL was epichlorohydrin, the concentration of epichlorohydrin tested would have been 0.1 nL/mL, which is 0.118 µg/mL [1]. This concentration is much lower than 3.6 µg/mL, the lowest concentration of epichlorohydrin tested in the mouse lymphoma TK assay (without S-9) (Jotz and Mitchell, 1981). The results for testing 3.6 µg/mL were not reported in that study, only the results for 71.5 µg/mL which was the epichlorohydrin concentration causing the maximum mutagenic effect. At 71.5 µg/mL, the mutation frequency was increased by a factor of 19 relative to the vehicle (DMSO) controls. However, since the maximum effect for epichlorohydrin was seen at 71.5 µg/mL, it is a reasonable assumption that no increase in the mutant frequency would be seen with epichlorohydrin tested at only 0.188 µg/mL because it amounts to just 0.2% of 71.5 µg/mL (and 3% of 3.6 µg/mL).

- 1,3-D and epichlorohydrin have been tested in *Drosophila* for the induction of sex-linked recessive lethal (SLRL) mutations. In the 1,3-D testing, a positive effect was reported using feeding for the route of exposure (Valencia *et al.*, 1985) (p. 337 of that study). Although Knaap *et al*. did observe a positive effect when epichlorohydrin was injected, no induction of SLRL's occurred when the exposure route was feeding (Knaap *et al.*, 1982). Likewise, Würgler and Graf (1981) reported no induction of SLRLs by epichlorohydrin when the exposure was done by feeding.

- 1,3-D and epichlorohydrin have been tested in comparable ways for induction of sister-chromatid exchange (SCE) in CHO cells without and with S-9. Loveday *et al*. (1989) reported that 30 µg/mL 1,3-D increased mean SCE's/cell by a factor of 1.7.

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[1] Assuming that the density of epichlorohydrin is 1.18 grams/mL = 1.18 µg/nL

This result was seen in testing without S-9 (26 hr exposure) as well as with S-9 (2 hr exposure). By contrast, Evans and Mitchell (1981) reported that epichlorohydrin at 19 µg/mL (0.0016% [2]) increased mean SCEs/cell by a factor of 3-4 (depending on the scorer) when tested without S-9 (21.5 hr exposure), but when tested with S-9 (2 hr exposure), the maximum effect was an increase by a factor of 1.6-1.8 (depending on the scorer) at 95 µg/mL (0.008%), with no increase occurring at 24 µg/mL. Therefore, epichlorohydrin, if present at 1% in the 1,3-D test material used by Loveday *et al*. (1989), is not sufficiently potent to have contributed significantly to the induction of SCE's seen in that testing of 1,3-D, regardless of whether S-9 is used or not used.

DAS's suggestion that "only the most relevant data-set, typically well conducted *in vivo* studies, for characterizing human risk should be used in making the assessment" does not negate the importance of positive genotoxicity results for the following reasons:

- The negative dominant-lethal testing reported by DAS may indicate that male germ cells were not affected by the 1,3-D inhalation. However, the negative results do not address whether the target tissues for oncogenicity in the same males exhibited clastogenicity (the presumed cause of mutation in germ cells in the dominant-lethal testing), just as the negative results ultimately do not address whether oocytes would have been affected had the dominant-lethal testing been conducted with females instead of males.

- The lack of induction of bone-marrow micronucleated polychromatic erythrocytes (PCE) using gavage exposure of CD-1 mice reported by DAS contrasts with the positive findings found by intraperitoneal injection of male B6C3F1 mice (the strain used in the NTP cancer bioassays) (Shelby *et al.*, 1993) and the induction of chromosome aberrations in bone-marrow cells by NTP (discussed in Appendix VI of the December 2015 RCD). In addition, Kevekordes *et al*. (1996) reported that oral exposure of NMRI female mice (but not males) resulted in an even stronger induction of micronucleated PCEs (MNPCEs) in bone marrow. These positive findings for micronucleus induction are not negated by the presence of 1% epichlorohydrin in the 1,3-D test material because epichlorohydrin has been negative in comparable testing using intraperitoneal injection of $\geq$ 100 mg/kg as the high dose (Kirkhart, 1981;

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[2] 0.0016 mL epichlorohydrin/100 mL culture medium = 16 nL/mL = 19 µg/mL

Salamone *et al.*, 1981; Tsuchimoto and Matter, 1981).[3] Also, the results with NMRI mice are internally consistent (males do not respond to either dose level whereas females respond to both dose levels) and the female responses are too strong[4] to be dismissed.

- In the case of the negative findings in the Big Blue mice, those findings may have resulted from testing that was not optimized for detecting a mutagenic effect (discussed in Appendix VI of the revised 1,3-D RCD). The transgenic-animal testing performed in 1996 was considered robust at the time. However, when considered in light of new OECD guidelines, the results from the Big Blue study of 1,3-D can be questioned for a variety of reasons, including dosing duration and levels and the lack of a "full," positive control (*e.g*., tumor induction from a known inhalation carcinogen).

- Finally, there are also positive *in vivo* effects using the alkaline elution procedure to detect the induction of DNA strand breakage in cells isolated from organs following acute oral exposure of rats to 1,3-D (Ghia *et al*. (1993); Kitchin *et al*. (1993); and Kitchin and Brown, (1994). These studies are discussed in depth in Appendix VI of the December 2015 RCD. Ghia *et al*. (1993) demonstrated dose responses for DNA damage in liver and gastric mucosa as well as positive findings in kidneys at the one dose level studied. Pretreatment with an inhibitor of cytochrome P450 decreased the DNA damage induced by 1,3-D in the liver, indicating that some of the DNA damage depended on metabolic activation. In Kitchin *et al*. (1993) and Kitchin and Brown (1994), DNA damage was induced in liver by a non-hepatotoxic dose of 1,3-D (e.g., no increase in serum alanine aminotransferase [ALT] activity, no decrease in P450 content). Also, results for 2-chloroethanol, iodoform, carbon tetrachloride, and chloroform confirm that chemicals that induce hepatotoxicity (increased serum ALT activity) do not necessarily induce DNA damage in this assay. Therefore, the DNA damage induced in liver by 1,3-DCP appears to result from genotoxicity and is not dependent on its producing cytotoxicity. Of note is no significant elevation in three serum hepatic enzyme activities (ALT, aspartate aminotransferase and alkaline phosphatase) with rats gavaged daily for three consecutive days with up to 100 mg/kg 1,3-D (Stott et al., 1997).

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[3] Salamone *et al.* (1981) in male B6C3F1 mice; Kirkhart (1981) in male ICR mice; and Tsuchimoto and Matter (1981) in CD-1 mice, both sexes.

[4] About 15 MNPCE's per 1000 PCE's in the treated females *versus* about 3 MNPCE's per 1000 PCE's in the vehicle-control females (pooled). In both tests, the mean frequency of MNPCE's in the treated females was about 5 times the mean frequency seen in the corn-oil females (Kevekordes *et al.* 1996).

- Attachment I identified the dose levels as 0, 12.5 and 25 mg/kg/day for rats and 0, 30 and 60 ppm for mice. However, Stott *et al*. (1997) indicated that there were five dose levels per species: 0, 5, 12.5, 25 and 100 mg/kg; and 0, 10, 30, 60 and 150 ppm. These same five dose levels per species were referred to in the DAS Comments. While the highest dose levels for the ^{32}P-postlabeling may have been 100 mg/kg and 150 ppm, their respective data were not submitted to DPR.

- Attachment I did not state how often the rats were gavaged or the mice were exposed by inhalation. Record 162471 (p. 16 of 241, Study Design) indicates that rats and mice used in the ^{32}P-postlabeling testing were dosed a total of 9 times over an 11-day period. The DAS Comments indicate that rats and mice were "sacrificed after 12 days of exposure." While in a poster presented by Dow scientists at SOT in 2015 ("Genotoxicity is Not a Key Event in 1,3-Dichloropropene-Induced Mouse Lung Tumorigenicity"), mice were exposed at 6 h/day, 5 days/week, for 3, 12 or 26 days and that lung tissue whose results were reported on the poster was taken after 3 days of exposure. Inconsistencies in the description of dosing and duration make it difficult to interpret the findings.

- Attachment I did not state when liver (rats) and lung (mice) were harvested relative to their last exposure. This is important given that DNA adducts would be expected to decrease over time due to removal by DNA repair enzymes and/or due to spontaneous loss of adducted-DNA bases. Stott *et al*. (1997) describes liver and lung harvested 24 hours following the final exposure as well as some mice sacrificed 2 hours after their third exposure. It is not clear whether these mice were used for ^{32}P-postlabeling testing. However, this is consistent with the narrative appearing in the 2015 SOT poster.

For both routes of exposure, the ^{32}P-postlabeling testing does not seem optimized to detect 1,3-D-derived DNA-adduct formation. (For the remaining discussion of the ^{32}P-postlabeling testing, highest dose levels are assumed to be 25 mg/kg and 60 ppm and that rats and mice underwent 5 dosing days, then 2 nondosing days, then 4 dosing days prior to sacrifice on study day 12 about 24 hrs after completion of the dosing.)

- Both dosing regimens (gavage and inhalation) seem too brief to achieve steady state for DNA-adduct concentrations. Beland and Poirier (1994) stated that a typical steady-state condition occurs after approximately one month of continuous dosing. Consistent with Beland and Poirier (1994), Walker *et al*. (1992) exposed

mice by inhalation to 100 ppm ethylene oxide (EO) for 6 h/day, 5 d/week, for 4 weeks and observed that DNA adduct concentration in lung approached steady state by 4 weeks of exposure. These authors also reported adduct half-lives of 2.3 and 1.0 days respectively for the lung and liver, indicating that a nonexposure for 1-2 days can significantly decrease the concentration of DNA adducts in major organs.

- To determine if there is 1,3-D-to-DNA adduct formation, testing levels should include the maximum tolerated dose (MTD) associated with the duration of exposure employed in the DNA-adduct studies. DAS states that high dose levels such as the MTD are above the physiologically relevant range and may result in exaggerated responses. As it stands, it is unclear whether: a) 1,3-D and/or its metabolites form DNA adducts; b) form DNA adducts not detectable by this version of ^{32}P-postlabeling; or, c) form DNA-adducts that were not detectable.

- A crucial aspect of DNA adduct studies is the inclusion of a positive control, especially when these studies fail to detect adduct formation. Ideally, the positive control should treat animals concurrently with a known DNA adduct forming chemical, use the exact same test and exposure conditions as used in the 1,3-D testing (same strain, sex, and age of test animals; same vehicle, same reagents, and methods to isolate, digest and radiolabel the DNA, etc.).

- In Attachment I, the positive control was reduced to salmon-testis DNA treated in a test tube with concentrated propylene oxide (PO) resulting in heavily modified DNA. The use of PO-modified DNA as the positive control mainly addresses only one facet of the investigation into DNA adduct formation, *i.e.*, the separation of radiolabel spots. We feel PO alone is insufficient as a positive control because it is a monofunctional alkylating agent because several known or expected 1,3-D metabolites are bifunctionally reactive (discussed in Appendix VII of the revised RCD including:
  - 1,3-D epoxide
  - 3-chloro-2-hydroxypropanal formed from the hydrolysis of 1,3-D epoxide
  - chloromethylglyoxal possibly formed from metabolic oxidation of 3-chloro-2-hydroxypropanal[5]

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[5] Since this is lactaldehyde with a chloro group at the 3-position, its metabolism may be by the enzyme(s) normally acting on lactaldehyde.

   o   3-chloroacrolein (highly reactive, bifunctional alkylating agent, and may
       have crosslinking activity) potentially formed by P450-mediated oxidation
       of 1,3-D or oxidation of 3-chlorallyl alcohol by alcohol dehydrogenase,
       catalase, or P450
   o   3-chloroglycidol possibly formed by epoxidation of 3-chlorallyl alcohol,
       among others.

Suffice it to say that negative findings with ^{32}P-postlabeling should be considered
provisional until it is demonstrated the reaction products of these metabolites with DNA
can be detected. This also suggests that variations in the ^{32}P-postlabeling method should
be tried, given that DNA-phosphate alkylation, DNA crosslinking, and cyclic guanine
adducts are presumably involved with 3-chloroacrolein and/or some of the epoxide
metabolites (Phillips, 2013).

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F.   REPRODUCTIVE TOXICITY
No DAS comments.

G.   DEVELOPMENTAL TOXICITY

Draft RCD
Page 76/Paragraphs 2&3: "As Telone was not in the food, it is unlikely that palatability was the
issue. It was plausible that the animals felt sickened after exposure to Telone and thus avoided
food. Water consumption was reduced only at the high dose, and only between gd 6 and 11."

DAS Comments:
While DPR claimed that water consumption was only reduced at the highest dosage, there was a
statistically significant reduction in water intake at the next lower dosage, also.

> **DPR-HHAB response:** Examination of Table III.14.b in the draft RCD (Table III.29 in
> the revised RCD) substantiates DPR's assertion that maternal water consumption in the
> rat developmental toxicity study was reduced only at the high dose.

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IV. RISK ASSESSMENT

A. Hazard identification

Draft RCD
Page 89/Paragraph 1: "A benchmark response (BMR) of one standard deviation (SD, 1σ), was used to generate the $BMC_{1\sigma}$ as well as a $BMCL_{1\sigma}$."

DAS Comments:
No justification is provided for why the lower confidence limit on the benchmark dose was derived for decrement in weight gain. The effect has a well-defined NOEL in each study, and weight gain decrement certainly doesn't reach the level of an adverse effect. The effect is also readily reversible, and required a minimum of 3 days before it was observed. Thus, we could understand the derivation of a $BMD_{1\sigma}$, but the BMDL for this effect is not justified. DAS provides an extensive discussion of the derivation of a benchmark dose for changes in body weight in Appendix B.

> **DPR-HHAB response:** The use of the lower confidence limit on the benchmark dose (or, in this case, the benchmark concentration) is standard practice in risk assessment. The BMCL is equivalent to a NOEL. Were we to set the critical value at the BMC, an additional uncertainty factor would be necessary. Use of the BMCL generates narrow confidence limits for well-designed studies conducted with high numbers of animals per dose group and wider confidence limits for those studies conducted with low animal numbers per dose group.

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Draft RCD
Table IV.1 Entitled NOELs, LOELs and BMD values…

DAS Comments:
It would be helpful to the reader if the NOELs and LOELs from these studies were listed.

> **DPR-HHAB response:** NOELs and LOELs were not included in Table IV because they did not add appreciably to the information in the table. The title was corrected in the

revised RCD to read "Benchmark concentration values based on body weight decreases after short term inhalation exposure of rats and rabbits to 1,3-D."

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Draft RCD
Page 91/HEC: "HEC = exptl. Concentration x (Da / Dh) x (Wa / Wh) x RGDR"

DAS Comments:
The Da/Dh factor implicitly assumes that ¼th the concentration for 4-fold longer duration produces the same effect, i.e., the effect is cumulative and irreversible. This approach may be appropriate for a genotoxic oncogenic endpoint, but it is not appropriate for a readily reversible endpoint such as weight gain decrement.

> **DPR-HHAB response:** The relationship between exposure time and concentration – an expression of the generalized form of Haber's Law (C^n x T = constant) – was considered to hold for 1,3-D. This is the position advocated by OEHHA in their Technical Support Document for determining non-cancer reference exposure levels (RELs) (OEHHA, 2008), as well as by USEPA, which made the same adjustment in its 2007 assessment (USEPA, 2007).

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Draft RCD
Page 91/HEC: "Some of the key assumptions fundamental to the use of the RfC methodology to derive a HEC based on systemic effects include: 1) all the concentrations of inhaled gas within the animal's body are periodic with respect to time (i.e. periodic steady state - the concentration vs time profile is the same for every week). Periodicity must be attained for at least 90% of the exposure."

DAS Comments:
The periodicity in the laboratory animal is NOT maintained for at least 90% of the exposure duration, because the animals are being exposed 5 of 7 days (71%). More importantly, there is no periodicity to the human exposure in that even the subchronic nearby field resident exposures occur as declining levels over a 2 week duration. The subchronic and chronic exposures are even more variable over time due to intermittent use and resulting exposure.

> **DPR-HHAB response:** We interpreted the periodicity to signify the attainment of a steady state air concentration within each exposure session. The concentration *vs.* time profile for each exposure week was best approximated by that assumption, even in view of the 5/7 day exposure regime.

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Draft RCD
Page 94/HEC: "HEC = (10 ppm) x (0.91) x (6 hr / 24 hr) x (5 days / 7 days) x (0.115) = **0.19 ppm**"

DAS Comments:
Same objection to use of Da/Dh factor as for body weight decrement. Very slight nasal epithelial hyperplasia is not an adverse effect, the effect is not the result of cumulative damage, because there is no indication that it becomes more severe over time nor does it progress to something more serious, and the effect is readily reversible.

> **DPR-HHAB response:** We retained the time factors in the revised document and note that USEPA made the same adjustment in its 2007 assessment (USEPA, 2007).

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Draft RCD
Page 95/Paragraph 2: "Both nasal respiratory and bladder lesions were LOEL determinants for chronic toxicity, suggesting both portal-of-entry and systemic routes of toxicity."

DAS Comments:
There is no chronic exposure of 1,3-D to humans and the calculation of a chronic risk is not appropriate. The Agrian PUR data demonstrates that application workers are handling 1,3-D at most 10% of the year (Appendix F). In any of the year-long monitoring studies, there were no

measureable exposures for most of the year, in large part because use in a given area does not occur year-round, and there can be no exposure if there is no proximate use. Also, as indicated in the previous 2 comments, the exposures that do occur do not result in irreversible effects and time averaging exposure over a year results in an artificial construct of actual exposure which is intermittent and of short duration.

> **DPR-HHAB response:** According to the AGRAIN PUR database, there were 11 months of use reported for Fresno County and 10 months of use reported for Kern County in 2014.It is important to note that in a year-long monitoring study in Merced, CA, measurable ambient concentrations of 1,3-D were detected in Township #5 throughout the year. Hence, it is appropriate to evaluate the chronic risk associated with 1,3-D exposure.

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Draft RCD
Page 96/Table IV.2.a: Columns for LOEL and NOEL contain the n/a (not applicable) symbol.

DAS Comments:
It is non-transparent and potentially misrepresentative not to show the LOEL and NOEL when they are available. Placing the LOEL and NOEL next to the derived BMCL will allow the risk manager to see the additional conservatism of utilizing this approach to characterizing hazard.

> **DPR-HHAB response:** The LOEL and NOEL values for the acute and short term studies were described in the study summaries (*e.g.*, Tables III.11 and III.18). The NOELs and LOELs for the subchronic and chronic studies were inadvertently left in the HEC array tables (Tables IV.4 and IV.5) of the revised RCD even after electing to base the seasonal and annual non-oncogenic risk on BMCL determinations.

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Draft RCD
Page 99/footnote g: "As no toxicity studies were conducted on young animals, this analysis had no way of assessing the possibility that infants and children might be more susceptible to the toxic effects of 1,3-D, hence the "database uncertainty" factor of 3."

DAS Comments:
Young animals were exposed in the developmental and reproductive toxicity studies, and there was no indication that they had increased sensitivity to the effects of 1,3-D.

> **DPR-HHAB response:** See our response to DAS's comment on pages 8-10 of this memorandum.

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Draft RCD
Page 102/Paragraph 4: "In addition, several metabolites and degradates of 1,3-D exhibit genotoxic properties."

DAS Comments:
Metabolites and degradates of 1,3-D technical were part of all toxicologic testing, and there is no basis to consider the toxicity of these metabolites and degradates independently.
The genotoxicity potential of metabolite and degrades of 1,3-D has been intrinsically assessed in in vivo studies. All guideline- and GLP- compliant in vivo studies showed that 1,3-D is negative in genotoxicity. Although minor metabolites suggest trace oxidative metabolism (epoxidation) pathway, no detectable epoxide was found in rodents at doses up to 100 mg/kg by gavage administration. 1,3-D was rapidly deactivated and adequate data suggest that measurable epoxidation of 1,3-D to epoxide, in the rodent, occurs only at high dose levels via non-relevant exposure route (*i.e*. ip administration) which result in lethality (Bartels *et al.*, 2000). Other isolated findings on metabolites or degrades are considered not relevant to in vivo situations.

> **DPR-HHAB response:** The genotoxic potential of 1,3-D metabolites is discussed on p. 28 in this memorandum and in Appendix VII of the revised RCD. Identification of such metabolites may clarify the nature of 1,3-D's tumorigenicity in lung and other tissues (see comments under Genotoxicity, starting on page 25 of this memorandum).

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Draft RCD
Page 103/Paragraph 1: "The SAC is the daily (8-hr TWA for the worker, and 24-hr TWA for the residential bystander) 1,3-D breathing-zone air concentration anticipated for the use season of the highest use county (i.e., 8 months for Fresno County from 2008-2012)."

DAS Comments:
Seasonal air concentration (SAC) is being used for calculation of intermediate term risk. Thus, the SAC might be the result of a 90 day average air concentration, but certainly not an 8 month use season. Detailed use information for shallow shank with/without tarp and drip with/without tarp (Appendix F) indicates that the season for these uses is short and amounts to less than 10% of a calendar year. This use data provides support for the correction of SAC and AAC concentrations to adjust for exposure frequency. Neither a residential bystander nor an occupational bystander is going to be adjacent to treated fields all over Fresno County. Specifically for occupational bystanders, most treatments do not occur during the harvest season, and most occupational bystanders are affiliated with a particular grower in one locale. Thus, the probability of co-location with a treated field at any given time is low, but assuming that co-location occurs even seasonally is highly improbable, and over the year impossible.

> **DPR-HHAB response:** The long-term exposure estimates (i.e., SAC, AAC, and LAC) for the occupational bystander were estimated according to ambient air concentrations of 1,3-D. Hence, workers are not anticipated to stay on the edge of a field every day of the 1,3-D use season in the county. However, the individual is anticipated to work within the county throughout the use season and thus may be exposed to the ambient levels of 1,3-D in the air during this time. As described in the final draft of the RCD, the mean of the 1,3-D air concentrations measured throughout Merced County over the estimated use season is used to estimate the SAC, AAC, and LAC for the occupational bystander (Rotondaro and Van Wesenbeeck, 2012).
>
> In the first draft of the RCD, the air concentrations measured in Township #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 township measured during the 8-month use season for Fresno County (incidentally 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 revised RCD, the measured air concentrations measured in 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 was less than that applied in the corresponding months in a higher use county for the same year (i.e., Fresno County).

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Draft RCD
Page 105/footnote c: "The worker is assumed to be located at the edge of the treated field during application for 8 hours. The air concentration utilized to generate this estimate was simulated at 3.04 meters from the edge of the field, the closest to the edge of the field in the simulation."

DAS Comments:
No worker is going to stay 3 meters from the edge of the treated field for 8 hr. Regardless of the work task, field workers are mobile, and virtually any work task will require moving from the edge of the field.

> **DPR-HHAB response:** Due to a lack of data on the typical field location(s) and duration(s) at each location for the various types of field-workers, a worst-case scenario was used to generate the short-term exposure estimate.

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Draft RCD
Page 105/footnote d: "This residential exposure scenario represents exposure which occurs at the edge of the 100-foot buffer-zone of a field treated once annually."

DAS Comments:
Are there any fields that are treated annually? As a result of cost of treatment with 1,3-D, crop rotation, repurposing use of the land, i.e., going from field crops to tree and vine or to commercial development, it is extremely unlikely that the same field will be treated annually for 70 years.

> **DPR-HHAB response:** Many strawberry fields are fumigated annually. Strawberries accounted for 21% of the 1,3-D use in California from 2008-2012. 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)" (*personal communication*, Steve Blecker, Pest Management & Licensing Branch, DPR, and Mark Bolda, UC Cooperative Extension-Santa Cruz County).

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Draft RCD
Page 106/Paragraph 3: "The wide range of values in this data set, however, generates an extremely large 95th %-ile value. To obtain a more representative value, the greatest outlier (*i.e.*, 41.09 µg/m^3), of the data set was dropped prior to calculating the 95th %-ile. The 95th %-ile value of the natural logarithm of the remaining 4 values is 8066 µg/m^3."

DAS Comments:
It is not clear why removing the lowest value of the 5 measurements would generate a lower 95th percentile. Since the calculated 95th percentile value exceeds the maximum measured value by 1.3-fold, the authors should clarify why they think this value is "more representative".

> **DPR-HHAB response:** In the revised RCD, the exposure estimates were generated using all five of the measured 1,3-D air concentrations.

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Draft RCD
Page 107/Table IV.5

DAS Comments:
The seasonal air concentrations are based on the assumption that a worker is involved in application 8 months per year. Thus, a single "average" worker could apply 8 months x 30 d/month x 171 lb/ac x 30 ac/d = 1,230,000 lb. As a result, one worker could apply half of all 1,3-D used in Fresno County in 2013, for example.

> **DPR-HHAB response:** In the final version of the RCD, the seasonal exposure estimates were revised using the latest 5 years of AGRIAN PUR data. Handler seasonal exposure estimates were based upon the use season and seasonal application rate calculated for the company applying the most 1,3-D using shallow shank, deep shank, or drip. Each use season and seasonal application rate was generated for the highest use county for the

application method of interest. Seasonal exposure was resolved down to the number of application days within the use season. Resolution of seasonal use down to the individual handler of the company, using reliable data, was not possible. As a result, the use seasons and seasonal application rates listed in the final version of the RCD were used to estimate exposure for the individual handler.

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Draft RCD
Page 109/Paragraph 1: "To derive the breathing-zone air concentration for the handler applying 1,3-D via the shallow-shank with the use of a tarp, the data set containing of the highest measured air concentrations for the 1,3-D applicator using shallow shanks without the use of a tarp but with the use of spillage controls was multiplied by the adjustment factor calculated above (*i.e.*, 3)."

DAS Comments:
Perhaps DPR can put this narrative in the form of an equation? Regardless of the logic, it is counterintuitive that an applicator could be exposed to a higher concentration of 1,3-D when using a tarp than without the tarp. For drip application, the measured ratio of tarp/non-tarp air concentrations of 1,3-D is $141/305 = 0.47$.

> **<u>DPR-HHAB response</u>:** The narrative was put in the form of an equation in the final version of the RCD.
>
> There were no measured air levels of 1,3-D with and without a tarp for drip irrigation. These air concentrations were derived from surrogate data obtained from chloropicrin worker exposure studies (Beauvais, 2010).
>
> The activity of a shallow shank applicator differs from that of the drip applicator. Moreover, the chloropicrin surrogate data used to derive the 1,3-D air concentrations for these exposure scenarios showed that the chloropicrin air concentrations for the broadcast shallow shank applicator using a tarp were higher than those for the broadcast shallow shank applicator not using a tarp. This observation may be an anomaly. However, due to a lack of data, these surrogate data were used to estimate exposure for the handler conducting 1,3-D shallow shank applications.

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Draft RCD
Page 113/Paragraph 1: "The 95th %-ile of these adjusted air concentrations is 4054 µg/m^3 or 0.9 ppm (Table IV.5)."

DAS Comments:
The problem with claiming this is a 95th percentile estimate is that there were several factors used as multipliers of the estimated 95th percentile air concentrations that were maximums. For example, it was assumed that the person would apply to the maximum number of sites observed in 3.1 hr extrapolated to 8 hr, with application at the maximum labeled rate.

> **DPR-HHAB response:** The estimate provided is the 95th percentile of the adjusted air concentrations. As such, it is an upper-bound estimate of the concentration to which applicators might be exposed. However, there is insufficient information to determine whether it is the 95th percentile of exposures actually experienced by applicators. The application rate and hours may exceed the 95th percentile, but we lack information about the percentiles represented by the measured air concentrations.

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Draft RCD
Page 113/annual air concentration: "To obtain the AAC, the SAC was multiplied by the use season of 8 months divided by the number of months in the entire year (i.e., 12 months)."

DAS Comments:
Implicitly assumed is that there is a person out there that makes applications using the "handwand" every working day for 8 months. Because the "handwand" is used almost entirely for replanting trees and vines in established orchards and vineyards, such an individual does not exist. For the same reason, it is unlikely that individual would treat an entire acre of planting sites (248 replant sites/acre) in any block of trees or vines, since they would have to move between sites that might be rows apart.

> **DPR-HHAB response:** In the revised RCD, the long-term exposure estimates (seasonal, annual, and lifetime air concentrations), were eliminated based on a lack of use data for the injection auger method in the AGRIAN PUR database.

The short-term air concentration for the worker using a "handwand" or injection auger is estimated using the maximum application rate. As stated earlier, the maximum application rate is not specified for this application method on either the product labels or CA permit conditions. Hence, the rate in pounds of AI/acre had to be estimated from the number of sites (tree-holes) an applicator could potentially treat in an 8-hr workday. As described in the EAD, due to a lack of data, this estimate and the exposure estimates were generated using surrogate data from a chloropicrin study.

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Draft RCD
Page 113/lifetime: "The LAC is obtained by multiplying the AAC with the number of years the handler is anticipated to work (i.e., 40) over the assumed lifetime of 75 years."

DAS Comments:
Using a "handwand" is a young person's job. It is unlikely you will find a person over 50 doing this type of very labor-intensive work.

> **DPR-HHAB response:** In the revised RCD, the long-term exposure estimates (seasonal, annual, and lifetime air concentrations), were eliminated based on a lack of use data for the injection auger method in the AGRIAN PUR database.

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V. RISK APPRAISAL

A. HAZARD IDENTIFICATION

Draft RCD
Page 114/Paragraph 1: "For short-term exposure estimation, the 1,3-D air concentration data from the site with the highest air concentrations were used."

DAS Comments:
Throughout the various work tasks, the field with the highest measurements was taken, then the 95th percentile of the distribution was derived, and then adjusted to the maximum label rate. This concentration is then implicitly assumed to occur for up to 3 consecutive days (since the effect

was observed only after 3 days minimum). Thus, DPR is using the upper bound air concentration on the upper bound application rate on the upper bound duration of exposure for short term. Does that represent anyone's actual exposure? Moreover the toxicologic endpoint chosen by DPR for short term is highly questionable (see Appendix E below).

> **DPR-HHAB response:** In the revised RCD, to assess short-term exposure, the 95th percentile was taken from the data acquired at all three sites of the study and not just the site with the highest 1,3-D air concentrations. Due to a lack of data, it is unknown whether the calculated 1,3-D breathing-zone air concentrations are the same as the actual highest exposures. However, for the short-term air concentration (STAC), the 95th percentile is calculated as an upper bound estimate (Frank, 2009) (*Note*: This reference was mistakenly left out of the references section of the revised RCD.)

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Draft RCD
Page 115/Paragraph 2: "The 95th %ile of the natural logarithm of these adjusted air concentrations is 170,459 µg/m^3 or 38 ppm (Table IV.5)."

DAS Comments:
This is supposedly an 8 hr TWA which is problematic, since the activity requires minutes rather than hours per field. Additionally, this concentration is well-above the olfactory detection limit, and is in the range producing narcosis. All of the products currently in use require a respirator for tarp removers. This is another example of an exposure estimated for a non-existent person. Please see Appendix G for a discussion of the derivation of a more realistic acute exposure value.

> **DPR-HHAB response:** See the response to the first DAS comment under "Exposure Appraisal", page 13 of this memorandum.

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Draft RCD
Page 120/footnote e: "SAC: Seasonal Air Concentration: air concentrations are estimated at 100 feet downwind from the edge of the field, using two-week flux modeling Johnson (2009b) and adjusted for mean application rate of 171.4 lb 1,3-D/acre."

DAS Comments:

The "seasonal" air concentration is estimated over a duration of 2 weeks. However, the subchronic effect was produced after 13 weeks of exposure. There is no data to demonstrate that the effect in rodents can be produced at a lower concentration for a longer duration, i.e., if a rat was exposed to (2/13) x 90 ppm ≈10 ppm, there was no effect; yet that is being assumed for humans. Especially as this is applied to nasal epithelial hyperplasia (an effect that is reversible over several weeks), the method DPR is using is incorrect. In actuality there is no seasonal exposure from a single application, since concentration is declining from shortly after application to 2 weeks post, and for the rest of the 13 weeks it is zero. It is unclear how DPR estimated seasonal air concentrations.

> **DPR-HHAB response:** We define seasonal exposure as a period of frequent exposure lasting more than a week but substantially less than a year, whether the exposure is constant or intermittent during the period (Beauvais, 2006). The two week 1,3-D flux was generated for consistency with previous fumigant exposure assessments (Cochran and Frank, 2010; Beauvais, 2012). In reality this is an underestimation. (Knuteson *et al.*, 1995; Knuteson and Dolder, 2000) showed that the fields continued to off-gas at the end of the monitoring period of 19-21 days. The method of estimating the seasonal air concentrations is described in detail in the text and in the footnotes to the table in section IV.B.3.a (Residential Bystander Exposures to Shank and Drip Fumigations).

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Draft RCD

Page 120/footnote h: "AAC: Annual Air Concentration: this estimate represents the air concentration amortized over the full year. It is equal to a single exposure of 14 days/365 days times the SAC."

DAS Comments:

Here DPR is assuming that an intermittent exposure of 2 weeks duration can be averaged over a year. The implicit assumption is that the effect is irreversible and cumulative when it is not. There is no AAC attributable to a single application, especially as it applies to nasal hyperplasia.

> **DPR-HHAB response:** The estimates for annual and life-time residential bystander exposures from nearby applications were removed from the revised RCD.

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Draft RCD
Page 120/footnote k: "LAC: Lifetime Air Concentration: equivalent to AAC."

DAS Comments:
Same objection as to derivation of an AAC.

>   **DPR-HHAB response:** The estimates for annual and life-time residential bystander exposures from nearby applications were removed from the revised RCD.

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Draft RCD
Page 133/Table IV.8

DAS Comments:
To the extent that DPR knows, an explanation for the approximately doubled air concentrations estimated by the HEE5CB model compared to the MCABLE model should be provided. Considering the conditional probabilities involved, it is a misnomer to characterize the LADEs as 95th percentile. For example, the location modeled represents the upper 2% of locations in the state in regard to use, and when estimating exposure to each gender, the probability is 0.5, so combined the estimates are for $0.02 \times 0.05 \times 0.5 = 0.0005$ or the 99.95th percentile of persons statewide.

Footnote b has a typo: "stimulations" should be simulations.

>   **DPR-HHAB response:** We have corrected the issue identified by converting all LADE back to LADD. The LADD values (mean and 95th percentile values) were direct outputs from the MCABLE and HEE5CB models. Also, we have added a sentence in the text to indicate that because the mobility assumption of HEE5CB dictates that the time of "moving in" starts from birth, the higher age-specific breathing rates and lower body weights of children than adults are expected to be major contributing factors to the higher LADD values generated by HEE5CB than MCABLE.
>
>   We have also corrected the typographical error noted by DAS.

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Draft RCD

Page 134/Paragraph 1: "For children, who are presumably exposed only under non-occupational scenarios, MOEs of 100 were considered to be health protective. The extra ~3-fold factor was due to database uncertainty arising because no toxicity studies were conducted on young animals. Consequently, we had no way of assessing the possibility that infants and children might be more susceptible to the toxic effects of 1,3-D."

DAS Comments:

The second sentence is factually incorrect, because the developmental and reproductive toxicity studies did include young animals. And the 3rd sentence is rationalization for using an unnecessary additional uncertainty factor to protect children from effects that are not adverse, e.g., decrement in body weight gain and nasal epithelial hyperplasia.

> **DPR-HHAB response:** No direct inhalation toxicity studies were conducted on neonates or young animals. Consequently, we retained the 3x uncertainty factor for children in the revised RCD. For more detail on this question, see our response to DAS's comment on page 9, paragraph 1 of the draft RCD above (pages 8-10 of this memorandum). In addition, it is important to reiterate that we considered the body weight gain decrements and nasal epithelial hyperplasia that drive the non-oncogenic aspects of the risk assessment to be adverse effects. In the case of the former, the approximately 5-10% decrement in weight gain compared to concurrent controls was consistently observed and indicated a failure to thrive under conditions of short term 1,3-D exposure. In the case of the latter, the hyperplasia was considered an indication of respiratory irritation.

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Draft RCD

Page 135/Table IV.9

DAS Comments:

It would be helpful for DPR to clarify why the "ambient" air concentration for short term in this table is greater than subchronic which is greater than chronic in the next 2 tables.

To ensure the proper perspective is provided, it would also be instructive to indicate with a footnote that an 80 acre field treated by shallow shank injection occurs in approximately 0.1% of 1,3-D applications. (See Appendix F.)

>**DPR-HHAB response:** The method of estimating the residential exposures from ambient air concentrations is described in detail in the text and in the footnotes to the table in Section IV.B.3 in the revised RCD.

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Draft RCD
Page 136/Table IV.10

DAS Comments:
As indicated previously, there is no seasonal exposure resulting from residing near the edge of a treated field. The estimated exposures are based on two week flux modeling applied to a 13 week toxicologic endpoint. Neither the method of estimating seasonal concentration nor the application of short term exposure to subchronic toxicity is valid.

>**DPR-HHAB response:** See the response to DAS's comment above on page 120/footnote e of the revised RCD, which appears in this memorandum on pages 44-45.

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Draft RCD
Page 137/Table IV.11

DAS Comments:
As indicated previously, there is no chronic exposure resulting from residing near the edge of a treated field. The estimated exposures are based on two week flux modeling amortized to a year. Neither the method of estimating seasonal concentration nor the application of short term exposure to chronic toxicity is valid.

>**DPR-HHAB response:** The estimates for annual and life-time residential bystander exposures from nearby applications were removed from the revised RCD.

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Draft RCD
Page 138/Table IV.12

DAS Comments:
There is no chronic exposure resulting from residing near the edge of a treated field. The estimated exposures are based on two week flux modeling amortized to a year. This calculation implicitly assumes that any damage that occurs in the 2 weeks of exposure resulting from residing near a treated field produces irreversible DNA damage that is not repaired, because the exposure is averaged over a year. Additionally, it is assumed that treatment of the nearby field occurs every year for a lifetime. This simply cannot occur. First, treatment of a given field does not occur every year for 70 years because no field is treated every year. Second, the field over an interval of 70 years will be repurposed due to crop rotation, planting to a more valuable tree or vine crop, or developed into housing or a strip mall.

> **DPR-HHAB response:** See the responses to DAS comments above on page 105/footnote d and page 120/footnote e of the draft RCD, which appear on pages 39-40 and 44-45, respectively of this memorandum. We will not speculate on the long-term repurposing of agricultural fields in California due to planting of other crops or development.

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Draft RCD
Page 138/Table IV.12

DAS Comments:
As noted in comments on Table IV.8, the exposure for the "high use area" is already at the 99.95 percentile. Assuming that cancer potency is estimated at the 95th percentile, the combined probability is at the 99.9998th percentile or 2 per 100,000. Since the intent was to regulate to the level of 1 in 106 persons, what DPR has actually done was estimated the risk for one individual in >106 persons.

> **DPR-HHAB response:** We revised the cancer risk calculations in order to address this comment.

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Draft RCD
Page 140/Table IV.14: The MOE for DPR's chosen short term toxicity endpoint (decrement in weight gain) is theoretically unacceptable for 2 scenarios: applicators using shallow shank with tarp, and occupational bystanders (shallow shank without tarp).

DAS Comments:
As noted previously, it is illogical to assume that exposure to the applicator is greater with a tarp than without. Because the toxicologic effect was not observed until the 3rd day, the short term application rate should be assumed to be the average rate and not the maximum label rate. Most applications do not occur at the maximum and to assume that it occurs daily for 3 days (especially for an occupational bystander chained to the edge of a freshly treated field each of those 3 days) is extremely unlikely.

> **DPR-HHAB response:**
> See the responses to the DAS comment on the draft RCD on page 13 of this memorandum and to the DAS comment on the draft RCD, page 109/Paragraph 1, on page 41 of this memorandum. Moreover, the short-term exposure estimates are intentionally upper bounds. These exposure conditions are not considered as being typical. For the occupational bystander, due to a lack of data on the typical field location(s) and duration(s) at each location for the various types of field-workers, a worst-case scenario (i.e., field-edge), was used to generate the short-term exposure estimate.

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Draft RCD
Page 141/Table IV.15

DAS Comments:
As noted previously, exposure is intermittent for any given handler. If DPR assumes that an individual is exposed each day for the season, that person could make all of the applications for that scenario for an entire county (or in some cases for the entire State). That simply does not occur.

> **DPR-HHAB response:** See the response to the DAS comment on the draft RCD, page 107/Table IV.5, which appears on page 40 of this memorandum.

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Draft RCD
Page 142/Table IV.16

DAS Comments
As noted previously, exposure is intermittent for any given handler, and there is no chronic exposure. If DPR assumes that an individual is exposed each day for the season, that person could make all of the applications for that scenario for an entire county (or in some cases for the entire State). That simply does not occur.

> **DPR-HHAB response:** See the response to the DAS comment on the draft RCD, page 107/Table IV.5, which appears on page 40 of this memorandum.

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Draft RCD
Page 143/Table IV.17

DAS Comments
As noted previously, exposure is intermittent for any given handler, and there is no chronic exposure. If DPR assumes that an individual is exposed each day for the season, that person could make all of the applications for that scenario for an entire county (or in some cases for the entire State). That simply does not occur.

> **DPR-HHAB response:** See the response to the DAS comment on the draft RCD, page 107/Table IV.5, which appears on page 40 of this memorandum.

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Draft RCD
Page 144/Paragraph 1: "Qualitatively, risk assessments for all chemicals have similar uncertainties."

DAS Comments
This is not true. Sources of uncertainty vary from chemical to chemical and use scenario to use scenario.

> **DPR-HHAB response:** This is a general statement that indeed has general truth. DAS's categorical statement ("this is not true") misunderstands its intent, which is precisely to say that, *qualitatively*, uncertainty varies "from chemical to chemical".

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Draft RCD

Page 144/Paragraph 2: "In the following sections, the uncertainties associated with characterization of health risks from exposure of workers and the general public to 1,3-D gas are described."

DAS Comments:

At various places throughout the document 1,3-D vapor is referred to as a "gas". Technically this is not correct.

> **DPR-HHAB response:** All references to "1,3-D gas" have been changed in the revised RCD to "1,3-D vapor".

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Draft RCD

Page 145/Paragraph 3: "Use of bodyweight decrement as a critical driver in risk assessment was accompanied by significant uncertainty, particularly with regard to the question of whether the observed weight decrements were of sufficient adversity to drive an acute / short-term health assessment. The operative assumption is that the animals emerged from the daily inhalation exposures with mild systemic illness rendering them uninterested or incapable of consuming as much food as unexposed controls."

DAS Comments:

As indicated in Appendix B, there are alternative methods of estimating the acute HEC without the need to speculate on a cause.

> **DPR-HHAB response:** This statement does not affect the estimation of the acute HEC. It remains in the revised RCD.

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Draft RCD
Page 145/Paragraph 4: "In the concentration range identified by the BMC modeling, the animals could have smelled the 1,3-D, considered it noxious, and thus curtailed feed consumption during the first few days of exposure."
DAS Comments:
This is interesting conjecture, but there was no reference provided to support it, *i.e.*, are there examples of animals reducing their food/water consumption after transient inhalation exposures to other chemicals above their odor threshold?

> **DPR-HHAB response:** We have uncovered possible causative relationships between odor and food-or-water consumption for two other chemicals that have undergone recent health risk assessments at DPR. While the exposure lengths may be different, they at least establish the plausibility of a relationship.
>
> 1) Chloropicrin: Food consumption was decreased in a 13-wk mouse inhalation study at 1.03 ppm (CDPR, 2012). In a human sensory irritation study, the odor threshold was 700 ppb and the NOEL for sensory irritation after one hour of exposure was less than 100 ppb (Cain, 2004). We assume that the odor threshold in mice is less than in humans.
>
> 2) Methyl bromide: Food consumption was decreased in a rabbit developmental toxicity study at 70 ppm (CDPR, 2002). The odor threshold for this chemical in humans is 21 ppm. While we don't know the rabbit threshold, we also assume that it may be even less than humans.

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Draft RCD
Page 145/Paragraph 4: "In the 10-week rat dominant lethal study of (Gollapudi *et al.*, 1998), 60 ppm and 150 ppm animals actually *lost* 1.7% and 6.5% of their body weight within the first 7 exposure days…"

DAS Comments:
Traditionally, body weight loss of 10% is considered adverse, while body weight gain decrement is not. Thus, it might be more useful if DPR discussed why they chose to use an effect rather than an adverse effect as their endpoint for acute/short term exposure.

> **DPR-HHAB response:** We consider a statistically significant weight gain decrement to be potentially adverse.

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Draft RCD

Page 146/Paragraph 2: "Furthermore, it was at least plausible that the body weight effect was NOT systemic in nature, but rather resulted from portal-of-entry impacts on the nasal passages and lung. While there were no experimental data to support this contention, longer-term exposures resulted in nasal and lung pathology, the very indicators used to calculate seasonal, annual and lifetime (oncogenic) risks."

DAS Comments:

The examples provided (acrolein and HCl) are both highly irritating and corrosive. They are not analogous in any way to the effects produced by 1,3-D in the respiratory tree. Longer term exposure of 1,3-D did produce measurable effects in the lung, but there is no evidence that the effects on the respiratory tree have anything to do with reductions in food and water intake.

> **DPR-HHAB response:** While 1,3-D may not be as irritative as acrolein or HCl, it is at least plausible that the body weight decrements caused by 1,3-D were related to that property.

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Draft RCD

Page 146/last paragraph: "In fact, the only experimental evidence for varied sensitivity was provided by Rick (1988), who determined the odor threshold for Telone II among 22 adults to range between 1.8±1.2 ppm through 16.0±1.5 ppm, reasonably close to the default 10-fold factor."

DAS Comments:

The range of odor threshold in humans is not a good measure of "sensitivity" for an effect, since by definition the population must be able to smell. Including nose-dead individuals in that range would increase the difference in "sensitivity" infinitely.

DPR-HHAB response: As stated at this point in the assessment, olfactory sensitivity is the only parameter we have to indicate the possible extent of interspecies variation with respect to this chemical. As such, we believe it important to mention here.

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Draft RCD
Page 147/Paragraph 1: "The mildness of the sign combined with its appearance in a distinct minority of animals suggested that it might not be sufficiently adverse to drive the seasonal risk evaluation. However, the fact that incidence reached 100% at 90 ppm, and severity had increased from "very slight" to "slight" by 150 ppm, suggested that it was indeed treatment-related and potentially adverse even at 30 ppm.

DAS Comments:
NAS (2015) made the following recommendation: "However, it is unclear how DPR defines an adverse effect on which those levels are based. The committee recommends that DPR clarify its definition and the criteria that it uses to make determinations." In the 1,3-D risk assessment, DPR is using "very slight nasal epithelial hyperplasia" as an adverse effect, apparently by rationalizing that it increased in incidence and severity (going from very slight to slight) at 90 to 150 ppm (concentrations at which there was undeniable adverse effects like body weight loss). However, it is unclear why very slight nasal epithelial hyperplasia is considered adverse. It has no effect on quality or longevity of life. It does not appear to progress to something adverse. Perhaps most concerning is that it would probably not be measurable at any level of 1,3-D exposure in the human population given the presence of oxides of nitrogen and ozone (among other irritants) in the air in the Central Valley of California. Ozone concentrations in air exceed the National Ambient Air Quality Standards for a majority of children in the US, and ozone is known to produce a continuum of nasal histopathology in humans and monkeys (Carey et al., 2011).

DPR-HHAB response: We view this effect as evidence of upper respiratory tract irritation. The observations that (1) the irritation gradually becomes more severe at higher doses, and (2) the incidence increases with dose support our view.

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Draft RCD
Page 149/last paragraph: "However, there is ample evidence both from *in vitro* and *in vivo* testing to suggest that 1,3-D is in fact genotoxic. These include positive indications in Ames-*Salmonella* testing, mouse lymphoma cells, and in inducing chromosomal aberrations in bone marrow and micronucleated polychromatic erythrocytes upon intraperitoneal injection into mice. In addition, several of the prominent 1,3-D metabolites are Ames positive."

DAS Comments:
As pointed out earlier (and in Appendix D), each of the "positive" studies was conducted at such high concentrations as to be unrepresentative of the dosages and resulting blood concentrations producing tumors in laboratory animals. Thus, until the body's defenses are overwhelmed (e.g., glutathione is depleted), there is no evidence that 1,3-D produces either genotoxicity or tumors. Further, as indicated previously, the Ames assay is a blunt tool that is not reliable in forecasting oncogenic effect.

> **DPR-HHAB response:** The demonstration of genotoxicity in standard assays, both *in vitro* and *in vivo*, combined with the lack of evidence for a threshold mechanism for lung adenomas, was sufficient to use the multistage linear extrapolation model to characterize the cancer dose response. It also bears mention that, with qualifications, the Ames assay correlates better with *in vivo* oncogenicity assays than the mouse lymphoma, chromosomal aberration and sister chromatid exchange assays (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). Please see responses to comments in the Genotoxicity section, on pages 25-32 of this memorandum.

^^^^^^^^^^^^^^^^^^^

Draft RCD
Page 150/Paragraph 2: "Finally, it should be noted that there was absolutely no evidence for preneoplastic foci in the mouse lung after 2 years of inhalation exposure to 1,3-D, despite the appearance of adenomas."

DAS Comments:
While there may be no evidence of pre-neoplastic foci in mouse lung, there was very clearly an inherent tendency to spontaneously produce lung tumors in this species and strain, and the same tumor type in the same location in controls is dramatically increased after more than a year of exposure at the highest dosage.

> **DPR-HHAB response:** Despite the evidence for spontaneous incidence, adenoma induction in the lung was also highly responsive to 1,3-D concentration in the inspired air. It was on this basis that we chose to model oncogenesis in this organ.

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Draft RCD

Page 151/Paragraph 1: "This runs counter to the more conservative estimates emanating from the multistage analysis, where all non-occupational and occupational exposure scenarios showed risk values above the negligible risk standard of 10^{-6}. Such a comparative analysis emphasizes the large uncertainties that are present when one or another mode of action is chosen to represent the actual biological situation."

DAS Comments:

The individuals that actually handle 1,3-D have higher risk, so the two methods of estimating risk agree in relative magnitude. Both USEPA and CDPR have used a negligible risk standard of less than 10^{-6} in the past for various residential exposures, and USEPA (1996) acknowledges that negligible risk for workers falls between 10^{-4} and 10^{-6}. Given that the average American has a 1 in 2 chance of developing cancer in their lifetime, what constitutes negligible oncogenic risk? The people of California voted to pass Proposition 65 that defined negligible risk as $\leq 10^{-5}$ for compounds known to the State to produce cancer.

> **DPR-HHAB response:** See the DPR-HHAB response to the DAS comment on the draft RCD page 10, paragraph 5, which appears on pages 10-11 of this memorandum.

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Draft RCD

Page 153/Paragraph 1: "This analysis did not assess the risk of metabolites and degradates, assuming instead that their appearance under the conditions present in the toxicity studies would be accounted for in the effects generated. Even so, an understanding of 1,3-D's toxicity is not complete without also understanding the toxic properties of metabolites, degradates and impurities, particularly as conditions in the field may conceivably affect the relative concentrations."

DAS Comments:
While we agree with the first sentence, the second sentence seems to be contradictory. Earlier DPR dismissed the presence of epichlorohydrin, a highly mutagenic carcinogen, as not being a likely factor in the NTP study results. DPR cited a 2 page "article" by Konishi et al. (1980) as the basis for that conclusion. Yet here they state the need to know "the toxic properties of metabolites, degradates and impurities." The potential conditions in the field that may contribute to their concern have not been elaborated with respect to how 1,3-D is handled per DAS' stewardship program. Further, while we know the metabolic pathways and rates of clearance in the rat are comparable to humans, we do not know that for mice.

> **DPR-HHAB response:** See the DPR-HHAB response to the DAS comment on the draft RCD, page 14/second to last bullet, which appears on page 12 of this memorandum.

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B. EXPOSURE APPRAISAL

Draft RCD
Page 154/Paragraph 1: "With the exception of the shank applicator using a tarp, this assumption led to the use of the corresponding 1,3-D data for estimating breathing-zone air concentrations for these handlers."

DAS Comments:
This exception apparently resulted in estimates for shallow shank injection with a tarp that were 3-fold larger than shallow shank without a tarp. Given that the only measured air levels of 1,3-D with and without a tarp was for drip irrigation application that showed the tarp reduced exposure 2-fold, the assumption appears to have created a 6-fold error. Further, 2 of 3 use scenarios for chloropicrin indicate that the tarp produces less exposure to the applicator than without a tarp.

> **DPR-HHAB response:** The exception referred to led to relatively lower 1,3-D air concentrations for the shallow shank applicator exposure scenarios (w/ and w/o tarp). The measured 1,3-D data used to estimate exposure for the shallow shank applicator (w/o tarp) were obtained from the portion of the registrant's 1,3-D study which utilized spillage controls. These measured air concentrations were lower than those measured during the applications conducted without spillage controls. The spillage control data were also used, along with the chloropicrin ratio approach, to derive the shallow shank applicator (w/tarp) exposure estimates. The cause of the roughly 3-fold higher breathing-

zone 1,3-D air concentrations for the shallow shank applicator (w/tarp) is the chloropicrin surrogate worker exposure data. These results show higher chloropicrin air concentrations for the shallow shank applicator (broadcast) using a tarp than for the corresponding applicator not using a tarp.

Also see the response to the DAS comment on the draft RCD, page 109/paragraph 1, which appears on page 41 of this memorandum.

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Draft RCD
Page 154/Paragraph 2:

DAS Comments:
Hand-wand application only occurs for tree replacement in established orchards, and is never used to treat an entire acre. As a result there is no seasonal, annual and lifetime exposure for this application scenario.

> **DPR-HHAB response:** See the response to the DAS comment on the draft RCD, page 5/last paragraph, which appears on pages 6-7 of this memorandum.

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Draft RCD
Page 154/Paragraph 3:

DAS Comments:
In addition to the required use of a respirator in any label currently in use, for tarp removers, they do not move from one application site to another because they are employees of the farm rather than the applicator. While the average tarped application site is approximately 20 acres, even a 40 acre site requires less than 3 hr for tarp removal. Thus, acute exposure is overestimated by 27-fold (8/3 x 10), and there is no seasonal, annual and lifetime exposure for this application scenario.

> **DPR-HHAB response:** Please see the response to the first DAS comment under "Exposure Appraisal" on page 13 of this memorandum.

According to county agricultural enforcement, the bulk of tarp removals are done by companies which specialize in this task. In rare instances, where the application site is extremely small, the tarp removal may be done by the local grower whose land is being treated.

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Draft RCD
Page 155/Paragraph 1: "Use of the reentry worker exposure study data conducted by the registrant may have led to estimates higher than the actual exposure for this worker."

DAS Comments:
The degree of overestimation bias can be approximated based on the relative flux rate at 3.8 and 7 days post-application. Because the decline is exponential, one can very safely conclude that the exposure is 2-fold less just based on a linear rate of decay.

> **DPR-HHAB response:** In response to this comment, an analysis of the flux profile for Field 1 broadcast shallow shank untarped application from the Gillis and Dowling flux study (Gillis, 1998) is presented below:
>
> 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.

Gillis and Dowling Vol50046-127 broadcast shallow untarp
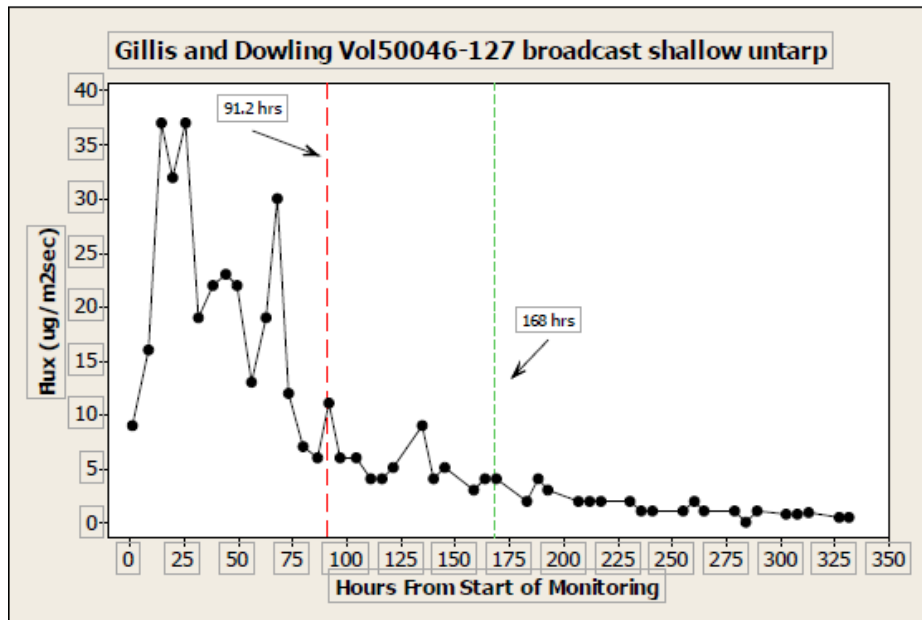
It is true that the general pattern of the flux profile is exponential decline after the first peaks are reached at 15 and 37 hrs. However, fitting that exponential would be difficult to impossible. TableCurve® software was used to fit the decline and, as expected, no acceptable fit could be found. There 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. In order for DAS's argument to be strictly correct all the flux values in that interval should be monotonically decreasing. However, it appears that 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 is 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, 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. DAS states that the difference is approximately a factor of 2, which is within the model uncertainty. This supports not changing the re-entry worker exposure estimates.

Closer examination at the portion of the entire flux profile that falls between 86.6 hrs and 168 hrs is shown below. The intervals immediately before and immediately after the 91.2 hrs and the 168 hrs were chosen, which is essentially what DAS did with the simple linear decline between 3.8 days and 7 days. A linear regression was fit through the data on natural log basis because DAS references a linear decline and that the flux is likely lognormally distributed. 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^{2}sec and 3.7 ug/m^{2}sec 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.
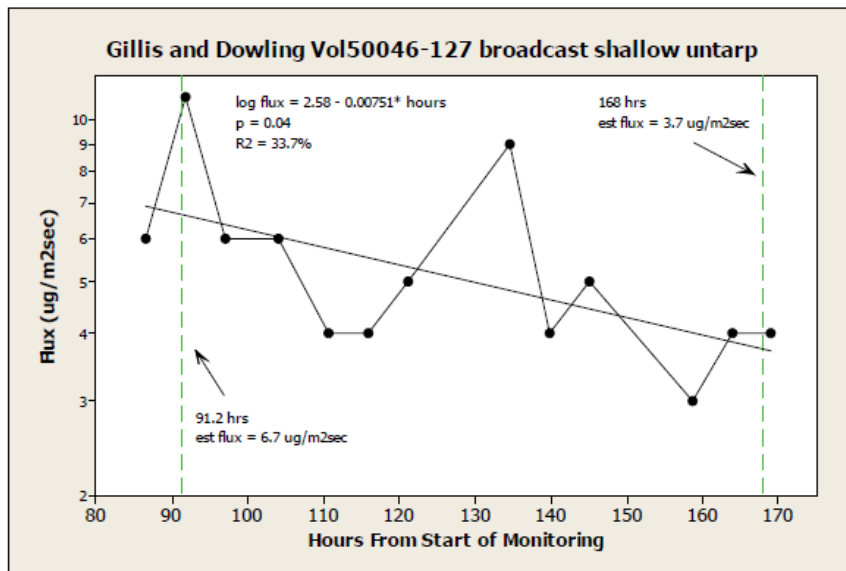
Given the lack of a monotonically decreasing flux profile in the area of interest (91.2 hrs to 168 hrs) , along with the resulting poor fit of the regression and the air dispersion model factor of 2 acceptability, it could be argued that it is not necessary to reduce the air concentrations used to estimate exposure for the reentry workers. Another potential source of uncertainty is the analytical variability of the study.

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Draft RCD

Page 155/Paragraph 2: "For estimating long-term breathing-zone air concentrations, the seasonal and annual means of the 1,3-D air concentrations measured in Receptor 5 of Merced County were utilized to estimate exposure."

DAS Comments:
This helps to explain why residential exposure is so similar to occupational bystander exposure. However, it is not clear why there is any difference. DPR should note that the air monitoring in Merced County was conducted under conditions where use deliberately exceeded the cap in several townships for research purposes (model validation). As a result, those data cannot be extrapolated to represent typical long-term exposures.

> **DPR-HHAB response:** The exceedance of the township cap during the Merced study was acknowledged in the assessment section of the draft RCD and in the assessment and appraisal sections of the revised RCD. The suspension of exemptions to the township cap was stated in Regulatory History section. We included a statement in the appraisal section of the revised RCD that the exposure may be overestimated when the township caps are observed. See the Residential bystander exposure sections in the revised RCD.

^^^^^^^^^^^^^^^^^^^

Draft RCD
Page 158/Paragraph 2: "All residential bystander exposures discussed in this document are 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. This presumption may lead to an overestimation of human exposure."

DAS Comments:
Also assumed is that wind is blowing toward the house, that there is no sink effect within the house, and that the house provides no protection to the person inside. The combination of conditional probabilities makes this scenario extremely unlikely and clearly overestimates exposure potential.

> **DPR-HHAB response:** Wind direction and whether a structure acts as a sink and/or a barrier, as well as other possibilities, are factors that potentially lead to an overestimation of human exposure. Insufficient data are available to determine the likelihood of combinations of factors.

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Draft RCD

Page 158/Paragraph 3: "Shallow shank applications were modeled for 80 acre fields for the purpose of this exposure assessment. This may not represent all or even the majority of field applications made on the most common crops receiving 1,3-D, and could lead to underestimates of the human exposure and risk."

DAS Comments:

For 2013, DPR's PUR indicates that of the 2936 applications made, 442 were made in Fresno County. Of those 442 sites, 20 were ≥80 Ac, and of those 20 sites, 8 were treated at the maximum label rate. Unfortunately, DPR's PUR does not indicate whether the applications were made as shallow or deep shank injections. Dow (2014) Agrian use data for Telone II shows that of 2886 applications Statewide there were 4 shallow shank applications made to ≥80 acres However, as indicated previously, DPR is assuming a series of conditions each with its own probability, i.e., that the field treated is ≥80 Ac and treated by shallow shank (probability = 0.00139), that it is treated at the maximum label rate (0.4) that there is a house located within 100 feet of the treated field edge, and that the wind is blowing toward the house from the treated field (1 in 4 or 0.25), that the house is occupied 24/7, etc. DPR is assuming that all of these conditions co-occur while the likelihood of co-occurrence is extremely low. For just 4 of the listed factors the probability is 0.000139 or 1 in 7,215. Since there were only 2,936 applications made in the entire State in 2013, DPR is essentially already limiting its characterization to a single field. Moreover, there is no subchronic or annual/chronic exposure to shallow shank-applied Telone whether that is handlers, reentry, or bystander.

> **DPR-HHAB response:** The AGRAIN PUR data provided by DAS allowed for detailed analysis of the 1,3-D use patterns in California over the last 5 years. A field size of 80 acres (or 40 acres for drip applications) and maximal application rate were used for modeling of short-term exposures, while the seasonal exposures were modeled for median field sizes and seasonal application rates in the revised RCD. The statement in question was removed from the revised text of the exposure appraisal.

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Draft RCD

Page 158/last paragraph: "Another source of uncertainty is the number of fumigations that a field could receive in one year."

DAS Comments:
There is no indication that any field is treated more than once per year, and many reasons why it would not, including cost, crop rotation, use cap, efficacy, pest resistance development, most labels prohibit it, etc.

   DPR-HHAB response: The statement in question was removed.

^^^^^^^^^^^^^^^^^^^

Draft RCD
Page 159/Paragraph 1: "Acute bystander exposure to drip application will be underestimated when the maximum label application rate for other sites is used: the InLine label allows for application rates on nursery crops up to 56 gal/a or 381 lb AI/a (capped at 332 lb AI/a per California Permit Conditions)."

DAS Comments:
InLine is 40% chloropicrin and should be applied with a tarp per label directions, although this was not mentioned.

   DPR-HHAB response: The label for InLine (33.3% chloropicrin) and the California
   Permit Conditions (Appendix K: Chloropicrin and Chloropicrin in Combination with
   Other Products (Field Fumigant) Interim Recommended Permit Conditions, revised April
   2015 http://www.cdpr.ca.gov/docs/enforce/compend/vol_3/append_k.pdf) do not
   explicitly require the use of tarps.

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Draft RCD
Page 159/last paragraph: "The Parlier study in 2006 showed that some 1,3-D ambient air concentrations may exhibit a potential of health concern (Wofford *et al.*, 2009)."

DAS Comments:
The potential health concern expressed by Wofford *et al.* (2009) was for potential oncogenic risk and not acute, intermediate or long-term risk. Additionally, because the Minimum Detection Limit in that study was so high, even non-detects were potentially of concern based on DPR's current negligible risk standard.

> **DPR-HHAB response:** The current 1,3-D RCD utilized data from the Merced study
> provided by Dow Agrosciences.

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Draft RCD
Page 160/Paragraph 2: "Collecting 72-hr samples in the Merced study most likely missed 24-hr
concentration peaks of 1-3-D."

DAS Comments:
While it is possible that the peak 24 hr concentration was missed, it is irrelevant. The short term
endpoint being used by DPR did not manifest until a minimum of 3 days post exposure. Thus, a
3 day average is appropriate for comparison to the endpoint used.

> **DPR-HHAB response:** The toxicological effect in the inhalation study of (Stott *et al.*,
> 1984) was not measured until 3 days after the dosing was initiated. The effect could
> conceivably have occurred earlier, before the first body weight measurement.

^^^^^^^^^^^^^^^^^^^^

Draft RCD
Page 160/Paragraph 2: "The missing sample could have been even higher than 369.2 $\mu g/m^3$."

DAS Comments:
If DPR is going to engage in such speculation, perhaps they should back it up with use data in
proximity to the sampler preceding the lost sample.

> **DPR-HHAB response:** In the revised RCD, the statement was modified to read, "These
> factors introduce uncertainty in the estimates of the short-term residential bystander
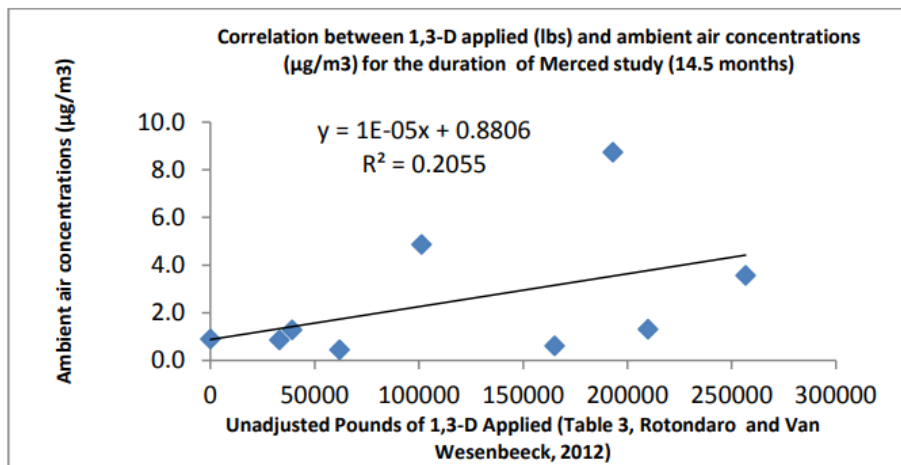> exposures to ambient air."

^^^^^^^^^^^^^^^^^^^^

Draft RCD
Page 161/Table V.4 footnote c.

DAS Comments:

When the ambient air concentration is greater than the estimated air concentration from treating a nearby field, is it possible that the ambient air concentration already includes the nearby treatment?

> **DPR-HHAB response:** As seen from the Merced study, the ambient air concentrations were elevated even in townships that received little or no 1,3-D during the year. The correlation between the recorded mean ambient air concentrations and the 1,3-D applied in the 9 contiguous townships for the duration of the study was not significant ($R^2 = 0.2$).

Correlation between 1,3-D applied (lbs) and ambient air concentrations (µg/m3) for the duration of Merced study (14.5 months)

$y = 1E\text{-}05x + 0.8806$
$R^2 = 0.2055$

Ambient air concentrations (µg/m3)

Unadjusted Pounds of 1,3-D Applied (Table 3, Rotondaro and Van Wesenbeeck, 2012)

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Draft RCD

Page 162/Paragraph 1 "As mentioned before, the EPA metric of the air concentrations for these scenarios was interpreted as "µg/m^3"."

DAS Comments:

Perhaps this would be a good place for DPR to explain why they are using ppb rather than µg/m^3. Since all of the measurements are made in µg/m^3, why does DPR convert those values to ppb?

> **DPR-HHAB response:** We used ppm as air concentration metric in the exposure assessment for consistency with the point-of-departures (PoDs) which were defined in ppm.

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Draft RCD
Page 162/Table V.5:

DAS Comments:
Why does DPR not list their estimates of long-term exposure in this table? It might also be interesting to a reader to know why EPA apparently did not estimate long-term exposures for shank and drip applications while DPR did, since this appears to be a significant difference between the agencies.

> **DPR-HHAB response:** DPR and USEPA have different definitions for short-, intermediate-, and long-term exposures. This was clarified in the appraisal section of the revised RCD. The following text was added to the appraisal section of the revised RCD:
>
> "For near-field sources (farmfields), EPA assessed only acute (24 hours) non-occupational bystander exposure scenarios for shank and drip applications. EPA acknowledged that at the time the Risk Assessment Document was prepared (2007) the computer models could not readily be used for exposures of longer duration (USEPA, 2007). Hence, the air concentration estimates generated by EPA and DPR were compared only for short-term (24 hour) scenarios".

^^^^^^^^^^^^^^^^^^^

Draft RCD
Page 163/last paragraph: "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. That is, only the simulation results with annual average values equal to or higher than the observed mean value were included. Accordingly, of the 100 lists of average annual air concentrations, 31 satisfied this criterion. Based on these lists of 31 average annual air concentrations, the highest exposure values from HEE5CB were presented in Table IV.8."

DAS Comments:
Footnote b in Table IV.8 says nothing about the parsing of data described in the quote to the left. The data in Table IV.8 are represented as "five cumulative probability distributions of average

annual concentrations…" Thus, the derived values in Table IV.8 apparently start as selected values greater than or equal to the observed mean values which are then recalculated as mean and 95th percentiles. We have already commented on the inappropriateness of expressing oncogenic risk as the 95th percentile when both the concentration and potency factor were at the 95th percentile. However, it now appears that the exposure estimated with HEE5CB was not the 95th percentile, but some upper bound of that number.

> **DPR-HHAB response:** We have corrected the issue identified by converting all values of LADE back to LADD. The LADD values (i.e., mean values) and the cancer potency value at 95th percentile were used to calculate the oncogenic risks of 1,3-D.

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D. CRITICAL TOXICOLOGIC ENDPOINTS: USEPA *vs*. DPR

Draft RCD
Pages 167-168/Table V.8

DAS Comments:
DAS notes some errors and omissions as detailed in the summary of regulatory endpoints we compiled in Appendix C [sic] of this document.

> **DPR-HHAB response:** We stand by the values in our "USEPA *vs*. DPR" summary table (Table V.6 in the revised RCD).

^^^^^^^^^^^^^^^^^^^^

VII.   REFERENCE CONCENTRATIONS

Draft RCD
Page 172/Paragraph 4: "Actual risk values ranged between 5.31×10^{-6} (nearby application site, edge of buffer zone, drip application, 40 acres) and 3.01×10^{-5} (ambient).

DAS Comments:

It is not clear where either of the quoted risk values is derived in the RCD. Table IV.12 indicates the nearby application site, edge of buffer zone, drip application, 40 acres risk is 5.4×10^{-6}, while there appears to be no place in the document supporting an ambient risk value of 3.01×10^{-5}.

> **DPR-HHAB response:** (The values that DAS cites on draft RCD page 172, paragraph 4 are actually in the Conclusions section (section VIII), not the Reference Concentration section (section VII).) These values have been changed in the revised RCD. However, we have discovered an error in the section alluded to by DAS which will be corrected in a future erratum. The paragraph in the Conclusions section (revised RCD, page 201) now reads:
>
> "All of the occupational and ambient lifetime exposure scenarios showed oncogenic risk values that were above the negligible oncogenic risk standard of 1×10^{-6} regardless of assumed mode of action. Occupational cancer risk values for a portal of entry mode of action ranged between 7.1×10^{-6} (occupational bystander near an application site, 3 scenarios) and 1.7×10^{-2} (tarp remover, deep shank); for a systemic mode of action they ranged between 2.4×10-5 (occupational bystander near an application site, 3 scenarios) and 5.6×10^{-2} (tarp remover, deep shank). Ambient cancer risks ranged between 2.30×10^{-6} (portal of entry, MCABLE, 30-yr fixed, female) and 40.44×10^{-6} (systemic, HEE5CB, birth to age 70, low mobility)."
>
> However, the values for "occupational bystanders near an application site, 3 scenarios" should read 1.9×10^{-6} (not 7.1×10^{-6}) for portal of entry and 6.6×10^{-6} (not 2.4×10^{-5}) for systemic. These will be corrected in an upcoming "Errata" document.

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Draft RCD
Page 173/Summary Table I

DAS Comments:

As we pointed out previously in discussion of footnotes on page 120, there is NO seasonal or annual exposure for residents near application sites. The toxicologic endpoint (nasal epithelial hyperplasia) is not produced at lower concentrations even over a lifetime, so whether assuming a 2 week exposure can be amortized over 13 weeks to estimate seasonal concentration or over a year to estimate chronic is not valid.

DPR-HHAB response: The estimates for annual and lifetime residential bystander exposures from nearby applications were removed from the revised RCD.

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Draft RCD
Page 174/Summary Table II

DAS Comments:
Oncogenic risk estimates calculated for the person living at the edge of the buffer zone are not valid. Those estimates are a subset of lifetime ambient exposures. Less than 0.01% of the population in high use areas will reside in the same house for their entire life, and no field will be treated each year for 70 years. The reality of crop rotation including repurposing to tree and vine crops, as well as economic development of agricultural land, competing fumigants and many other factors preclude a lifetime of annual use of 1,3-D on one parcel. The combined probability of a person living in the same house on the edge of a field treated with 1,3-D annually for a lifetime is infinitesimally low.

DPR-HHAB response: See the responses to comments on page 105/footnote d (this memorandum, page 39), page 120/footnotes e, h and k (this memorandum, pages 44-46), and to the first comment on page 138/Table IV.12 (this memorandum, page 49).

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VIII.   DAS comments in Appendices

Appendix G: Exposure estimates for occupational and non-occupational scenarios

The comments expressed by DAS concerning the handler exposure estimates were addressed in previous responses.

The DPR modeling used to generate both the worker and bystander exposure is based upon screening modeling methods for worker exposure described in (Barry, 2008). Prior to the development of the screening modeling methods DPR did rely on measured air concentrations alone to estimate worker exposure. Suggestions to use the flux estimation center mast air concentrations on which to base the 1,3-D worker exposures exposure estimates suffer the same limitations as the use of any other measured air concentrations. Measured air concentrations are a snapshot of air concentrations at that location at that moment only. Modeling methods are used

generalize those very specific results to other conditions. The screening modeling methods developed and presented in (Barry, 2008) and implemented for 1,3-D worker exposure estimation in (Johnson, 2009) are specifically intended to yield the reasonable worst case air concentrations for a particular scenario. The reasonable worst case captures expected air concentrations associated with the labeled largest application size and rate occurring under the standard screening meteorological conditions.

The standard screening meteorological conditions are based on the averaging time of the health threshold. For 1,3-D the two averaging times of interest are 24 hr and 8 h TWA. The screening meteorological conditions were previously developed by DPR (Johnson, 2005), and (Barry, 2004). With regard to the screening meteorological conditions, it is incorrect to state that a constant wind speed and direction blows "… in the direction of the worker for the entire 8 hour period." The air concentrations estimated with the screening method are directly related to the averaging time of the flux. The 8-hr flux is a time weighted average and thus, captures the variability in the wind direction and speed during the sampling interval. This same wind direction and speed variability is implicitly captured in the air concentration estimated using that 8-hr TWA flux. The wind direction over the 8-hr (or other averaging time) must be interpreted only as a predominant or average wind direction. It is reasonable to assume that a worker could be exposed to such a condition.

DAS (page 69, Appendix G): First, the same fields are not treated every year, for 70 years.

> **DPR-HHAB response:** See the response to comments to Page 105/footnote d, which appears on page 39 of this memorandum.

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DAS (page 70, Appendix G): Finally, per CA PUR data, only a small percentage of treated fields are actually >80 acres (See also Appendix F).

> **DPR-HHAB response:** 80 acre field size (shank applications) was used in the revised RCD only for estimating short-term occupational and residential bystander exposures.

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DAS (page 71, Appendix G): CDPR used concentrations of 1,3-D in air measured as part of the Merced monitoring study (Rotondaro and Van Wesenbeeck, 2012) to determine the short-term, seasonal, and annual exposure estimates for ambient air. The Merced monitoring study was

conducted for the purpose of model validation and hence had an unusually large quantity of 1,3-D applied (under special exception by DPR for research purposes), especially during the months of December, to ensure measureable quantities of 1,3-D and to enable the investigation of air concentrations and air dispersion model performance during atmospherically stable (calm) periods. Therefore, these values are not representative of potential human exposure and not appropriate to use in risk assessment.

> **DPR-HHAB response:** See the response to comment to Page 155/Paragraph 2, which appears on pages 62-63 of this memorandum.

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