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SUBJECT: Response to comments by US EPA on DPR-HHAB's draft 1,3-Dichloropropene Risk Characterization Document dated August 31, 2015

Following a review of the draft 1,3-Dichloropropene (1,3-D) Risk Characterization Document dated August 31, 2015, US EPA submitted answers to specific risk assessment and exposure issues presented to them by the Human Health Assessment Branch of the Department of Pesticide Regulation (DPR-HHAB). The following paragraphs provide each risk assessment issue, US EPA's answer to each issue, and DPR-HHAB's response to each of US EPA's stated answers.

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

HED comment: HED does not agree with the use of bodyweight decrements measured at 3 days from the 13-week inhalation study as the basis for the acute inhalation point of departure (POD). Based on HED policy, these bodyweight decrements are not considered to be sufficiently adverse, even at exposures of 150 ppm. HED's current policy uses a 10% decrease in absolute

bodyweight as a threshold for determining adversity. In addition, HED prefers to use studies that more accurately match the acute exposure duration, and thus, are more appropriate for use in the acute inhalation risk assessment.

> **DPR-HHAB response**: We used a reduction in body weight gain compared to concurrent controls to characterize acute / short term risk because it was an effect that was consistently observed through several studies in rats, mice and rabbits. The use of the $BMCL_{1\sigma}$ to model weight deficits was in conformance with US EPA's recommendations for analysis of continuous data (body weight, in this case) compared to those controls. We considered the $BMCL_{1\sigma}$ to adequately represent a critical NOEL value.
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> US EPA's stated practice of considering a 10% decrease in absolute body weight as a threshold for adversity may allow less severe, though adverse, effects to be unregulated. HHAB does not consider this practice to be adequately heath protective. It is also relevant to note that HHAB chose to combine acute and short term exposure scenarios rather than considering them separately as US EPA did in its own 1,3-D assessment (USEPA, 2007). We felt that the distinction between strictly acute and short term (1-7 days) exposure scenarios was too difficult to resolve, particularly when actual human exposures do not fall neatly into one or the other duration.
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> Finally, when considering short term (as opposed to strictly acute) toxicity, US EPA based their NOAEL of 20 ppm on a reduction in body weight gain in a rabbit developmental toxicity study (USEPA, 2007). This value was reasonably close to HHAB's acute / short term value of 49 ppm.

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Risk assessment issue #2: The effect of 1,3-D on bodyweight was assumed to be systemic in nature, implying that it had to be absorbed into the blood and distributed throughout the body before it could cause the effect. Because of this, we used the U.S. Environmental Protection Agency's (U.S. EPA's) recommended regional gas dose ratio (RGDR) default scalar of 1 to calculate the human equivalent concentration. However, there are uncertainties that accompany the assumption of a systemic mode of action, not the least of which is the possibility that the bodyweight effect could be mediated at the portal of entry, thus not requiring absorption or distribution. If, for example, the effect was mediated at extrathoracic sites---as was the case for the subchronic and chronic critical endpoints---then the RGDR would be significantly LOWER than 1, with consequent effects on the human equivalent concentration (HEC). On the other

hand, if it was mediated at pulmonary sites, the RGDR would be much GREATER than 1. In light of these considerations, please comment on whether the assumption of a systemic mode of action is justified.

HED comment: HED also considered decreased bodyweight as a systemic effect and utilized an RGDR of 1 when calculating HECs for 1,3-D.

DPR-HHAB response: No response necessary.

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

HED comment: HED also decided that the use of the RGDR approach allowed for the reduction of the pharmacokinetic uncertainty factor to 1x, resulting in a total interspecies uncertainty factor of 3x.

DPR-HHAB response: No response necessary.

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Risk assessment issue #4: The critical chronic NOEL of 5 ppm (hyperplasia of the murine nasal epithelium at 20 ppm) was adjusted to human equivalent concentrations of 0.16 and 0.49 ppm for non-occupational and occupational scenarios, respectively. The RGDR of 0.198 used to make this conversion was based on an extrathoracic portal of entry mode of action. However, bladder effects were also noted in the critical study, demonstrating that in addition to a portal of entry effect, 1,3-D also had systemic effects under chronic conditions. As noted above, a default RGDR of 1 is recommended in the case of systemic effects. Had we opted to base the critical chronic value on bladder effects, the human equivalent concentration would have been ~5-fold higher. Please comment on whether it is appropriate to base the chronic health assessment on the relatively slight extrathoracic effects (resulting in lower HECs) than on the systemic effects.

HED comment: Similar to CDPR, HED utilized an RGDR of 0.204 when calculating HECs for this study. This resulted in a health protective HEC that was the most appropriate for longer-term inhalation risk assessment.

DPR-HHAB response: HHAB opted to evaluate chronic toxicity using a $BMCL_{10}$ of 6 ppm rather than a NOEL of 5 ppm in the revised RCD dated Dec. 31, 2015..

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Risk assessment issue #5: There are reasons to question the multistage linear extrapolation approach for inhaled 1,3-D-induced lung tumors. Most importantly, the incidence curve for bronchioloalveolar adenomas---9/49, 6/50, 13/49 and 22/50 at 0, 5, 20 and 60 ppm---suggests the existence of an effective threshold for tumor production. In this view, very low concentrations of 1,3-D would not induce tumors since the organism has the presumed capacity to detoxify the chemical through metabolism and/or excretion. Please comment on whether it is appropriate for DPR-HHAB to use a linear extrapolation model to characterize the oncogenic risk of 1,3-D.

HED comment: HED agrees that it is appropriate for DPR-HHAB to use a linear extrapolation model to characterize the carcinogenic risk of 1,3-D. Regardless of the shape of the dose-response curve, the 2005 EPA Guidelines for Carcinogen Risk Assessment require defaulting to a linear extrapolation approach in the absence of definitive mode-of-action data supporting a nonlinear mechanism of tumor formation. The 1,3-D incidence data for induced bronchioalveolar adenomas may appear to have an effective threshold, but without data supporting a clear mode of action it is impossible to determine whether there is a threshold for tumor formation, or that the statistical power of the study is insufficient to see the linear response. This uncertainty combined with positive evidence of mutagenicity requires the quantitative cancer assessment to assume a linear approach.

DPR-HHAB response: No response necessary.

Exposure Assessment Issue #1: Handler Exposure – Please comment on the surrogate approach used to generate the exposure estimates for the following handler scenarios: a) applicator (shallow shank w/ tarp); b) applicator (drip w/ tarp); c) applicator (drip w/o tarp); d) applicator (hand-wand); and e) tarp remover.

HED comment: In general, HED utilized a similar handler exposure dataset in the most recent 1,3-D risk assessment as CDPR. CDPR did utilize surrogate chloropicrin data for the five scenarios listed above. HED does not believe this is an appropriate risk assessment approach as 1,3-D and chloropicrin off-gas at different rates.

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

HED comment (continued): In addition, as a result of using the chloropicrin data, the air concentrations presented in Table IV.5 in CDPR's assessment do not compare well across scenarios. For example, the 1,3-D data for shallow shank w/o tarp result in a STAC of 0.5 while the shallow shank w/ tarp result in a STAC of 1.6 when in reality it would be expected that a shank w/tarp application should result in lower air concentrations.

DPR-HHAB response: This observation may be an anomaly. However, due to a lack of 1,3-D specific data, chloropicrin surrogate data were used to estimate exposure for the handler conducting 1,3-D shallow shank applications (Beard, 1996; Rotondaro, 2004; Beauvais, 2010a). As explained in the draft RCD, data collected at the Arizona site in the Beard et al. study were not used to generate the chloropicrin ratios because the applications did not meet the good agricultural practices requirement on the federal label (Barry, 2014).

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Exposure Assessment Issue #2: Residential Bystander Exposure – Two human stochastic exposure assessment models were used to evaluate the lifetime exposure to 1,3-D by individuals residing in a high 1,3-D use area: Monte Carlo Annual-Based Lifetime Exposure model (MCABLE) and High-End Exposure version 5, Crystal Ball (HEE5CB). Please comment on the modeling approach taken in this risk assessment to characterize the exposure and cancer risk estimates of 1,3-D.

HED comment: In the 2007 Phase 5 risk assessment, HED utilized CARB and TAC data to examine lifetime ambient air exposures. The approaches used by CDPR appear to be based in good science but appear to be more appropriate towards the township specific approach that CDPR has adopted rather than HED's nationally based assessment. It does seem that the lifetime daily exposures presented in Table IV.8 are orders of magnitude higher than the values shown in the CARB data. Some explanation of the potential reasons for these order of magnitude differences would provide for a more complete risk assessment.

> **DPR-HHAB response**: The purpose of this 1,3-D assessment is to evaluate the health risk associated with inhalation exposure to worker, bystanders, and the general public in California. Accordingly, the stochastic human exposure assessment methods employed are consistent with the township approach adopted in California and may not be applicable to other states. The 1,3-D exposure estimates (and therefore the cancer risk estimates) were based on Merced, CA data, which is considered a high-use area for 1,3D. Therefore, the conclusions should be applicable not only to Merced but to other California townships with similar or lower use level of 1,3-D and similar weather patterns.
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> As stated in the draft RCD (page 132), Table IV.8 shows the estimates of lifetime average daily exposure (LADE) of individuals living (1) variable times of, (2) 30 years of, (3) 50 years of, or (4) 70 years of a total 70-year exposure/lifetime in a high 1,3-D use area using MCABLE. In this risk assessment, all exposure values are presented as air concentrations in parts-per-billion (ppb). Accordingly, the LADD values estimated by HEE5CB and MCABLE are converted into LADE for consistency in presentation.
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> Ambient air monitoring conducted by CARB generally targets high-use areas during times when use is expected to be high. However, in at least some cases the highest use may not be captured; an example of this is given in Beauvais (2010b). The LADE are considerably closer to concentrations measured by the registrant in Merced (Rotondaro and van Wesenbeeck, 2012). Thus, the discrepancy between LADE and concentrations that have been measured in high-use areas is less than it would seem if only CARB air monitoring is considered.

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Exposure Assessment Issue #3: Please comment on the approaches used to estimate the seasonal and annual 1,3-D air concentrations for the shallow shank, deep shank, and drip application methods.

HED comment: It is unclear to HED why CDPR utilized a nominal flux rate of 100 $\mu g/m^2/s$ for all applications and all field sizes. In the 2007 Phase 5 risk assessment, HED modeled 10 separate flux studies utilizing a variety of application equipment as well as modeling multiple field sizes and meteorological conditions. Most of these flux studies showed significantly lower fluxes than the nominal 100 $\mu g/m^2/s$ used by CDPR with many studies having fluxes an order or two orders of magnitude lower. Did CDPR consider use of these flux studies for modeling residential bystander acute and short-term air concentrations?

> **DPR-HHAB response**: The nominal flux of 100 $\mu g/m^2/s$ was utilized as a generic unit metric for calculating a generic air concentration for all applications and all field sizes. This approach allows for scaling up or down of the air concentration to adjust for application rate which reflects the respective exposure scenario. For the same exposure scenario (e.g., application method, field size, meteorological conditions), it is not necessary to rerun the model for each application rate of interest. The assumption is that flux is directly proportional to the application rate and that air concentrations are directly proportional to the flux (Barry, 2014). The Gaussian Plume Model produces air concentrations that are directly proportional to the flux. The nominal flux is 100 $\mu g/m^2/s$, which is not the flux measured in any particular flux study. However, the air concentrations output from the single ISCST3 model run using the 100 $\mu g/m^2/s$ can be easily adjusted to the air concentrations that would have been obtained for any flux of interest. This approach is also a useful tool for creating mitigation strategies. The short-term and sub-chronic flux derived by DPR was measured in the registrant studies cited in (Johnson, 2009b; Johnson, 2009a).

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