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DATE: September 8, 2016

SUBJECT: Responses to comments by Dr. Urmila P. Kodavanti on DPR-HHAB's draft 1,3-Dichloropropene Risk Characterization Document dated Aug. 31, 2015

Dr. Urmila P. Kodavanti submitted comments on DPR-HHAB's draft 1,3-D Risk Characterization Document in a memorandum dated November 17, 2015 (SWRCB, 2015). The following paragraphs provide those comments which were based on the charge questions posed to reviewers by DPR-HHAB, along with DPR-HHAB's detailed responses.

Hazard Identification and Risk Assessment

Dr. Kodavanti comment: *1) The bodyweight decrement was selected as a critical endpoint in the acute risk assessment of 1,3-D:* All available toxicology data on 1,3-D are adequately summarized in the document and the consideration of body weight gain decrements by 1,3-D as a critical endpoint for risk assessment is well justified. There is ample evidence to support that body weight decrements is the most consistent finding. However, the available data are not sufficient to support the assumption that the decrease in body weight gain is due to systemic effects from translocation of 1,3-D and its metabolites to extra pulmonary organs. Systemic effects can occur as a result of lung, nasal effects and/or respiratory tract effects without the need for chemical translocation to extra pulmonary organs from the lung. Although the data support systemic translocation since 1,3-D metabolites are detected in urine; body weight decrements can be an independent effect secondary to the respiratory tract irritation-mediated activation of a systemic stress response. The concentration-dependent effects data demonstrate that the body

weight decrements can occur at levels where pathological changes in the nasal and pulmonary epithelium are evident, which justifies the use of these endpoints for further consideration in risk assessment.

DPR-HHAB response: We critically evaluated the possibility that the body weight effects were mediated at the respiratory portal of entry and discussed this possibility in the Risk Appraisal section of the draft RCD on page 146. The relevant passage also appears in the revised RCD on page 175 and is quoted in full here:

"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 indicators used to calculate seasonal, annual and lifetime (oncogenic) risks. There was precedent for a predominantly respiratory system impact leading to body weight decrements. Fischer 344 rats exposed to gaseous acrolein, a closely related chemical, exhibited body weight gain decrements without clear systemic toxicity at the doses employed (Dorman *et al.*, 2008). Upon removal from the daily exposure regimen at 13 weeks, body weights immediately began to correct toward control values, suggesting respiratory irritation as the basis for the effect. In another study, tracheal instillation of hydrochloric acid in C57BL6 mice resulted in body weight loss accompanied by several indicators of lung injury including decreased oxygenation, increased respiratory elastance, pulmonary inflammation, alveolar-capillary barrier dysfunction and epithelial injury (Patel *et al.*, 2012). Here too, the body weight effect probably stemmed from the initial respiratory tree impact. Calculation of the HEC for a portal-of-entry mediated effect could have invoked a rat-to-human whole-lung RGDR of 2.91 (calculated for male rats), thus raising the HEC and MOE by that factor. Or if an extrathoracic impact was sufficient to impact body weight, the RGDR would have been closer to 0.1. The default systemic RGDR of 1 obviously fell between these two possibilities."

While the data did not exclude a portal of entry mechanism, we felt that, in view of the pharmacokinetic evidence for absorption, a systemic mechanism more likely drove the body weight effect.

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Dr. Kodavanti comment (continued): The decrements in body weights for 1,3-D are concentration-dependent in acute, subchronic and chronic studies. The reversibility of this effect

after a short non-exposure period is critical, especially for the exposure scenarios that relate to seasonal high levels of episodic exposures to 1,3-D. Acute studies depicted in the document demonstrate that body weight loss after an acute 1,3-D exposure is reversible during no exposure periods, but this aspect is not discussed in detail. The animal studies using episodic exposures simulating worker or bystander exposure during 1,3-D field applications are lacking, and therefore, the potential health consequences of such exposure scenarios cannot be accurately predicted. A onetime high dose effect observed episodically during each application in an occupational or bystander exposure can have more profound biological consequences than low levels of continuous exposure. Or, for non-cancer effects, there might be an adaptation to subsequent exposures. There is no information available from prior studies to show if there is an adaptation. The available data from acute and long-term studies of 1,3-D dose-related body weight decrements will not provide information of the adaptability and reversal of effects of 1,3-D during non-exposure periods. Thus, although scaling is used for exposure assessment of concentrations for long-term (annual and lifetime), based on highest levels detected in the breathing zone during each application, the realistic annual and lifetime exposures might be the primary driver of changes in the body weights, epithelial degeneration and perhaps the oncogenicity. The effects of very low levels of continuous 1,3-D exposure have not been studied; which can limit the predictability of health effects based on estimates for lifetime continuous low level exposures.

> **DPR-HHAB response:** We agree that the conditions imposed on laboratory animals don't adequately replicate the conditions in the field particularly with respect to episodic exposures and reversibility, and acknowledge that there are inherent difficulties and uncertainties with interpreting standardized laboratory studies in order to glean their relevance to actual human exposures.

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Dr. Kodavanti comment (continued): *2) The effect of 1,3-D on body weight was assumed to be systemic in nature ... RGDR was used for determination of HECs:* The body weight decrement effect is presumed to be due to systemic translocation of parent cis- and trans-isoforms of 1,3-D and its metabolites that have been detected in urine. It is presumed that once inhaled or ingested, 1,3-D is rapidly distributed systemically. However, it is likely that body weight decrement might not be due to systemic translocation, but rather the result of respiratory irritation-mediated systemic stress response, which can lead to metabolic derangement in multiple organs affecting body weights. The long-term data are adequate to support the presumption that respiratory irritation and the bladder epithelial hyperplasia are due to local irritation because of the

translocated metabolites. The use of RGDR allows for estimation of HEC and thus, the reduction in uncertainty factor to 3 from original 10 generally used for animal to human extrapolation.

DPR-HHAB response: See our response to comment #1 above.

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Dr. Kodavanti comment (continued): *3) Due to RGDR approach the conventional risk factor of 10 was reduced to 3.* The reduction of uncertainty factor to 3 is appropriate when using RGDR and is in line with what has been used by the US EPA. The retention of uncertainty factor 10 for protecting susceptible populations including children is appropriate.

DPR-HHAB response: No response is necessary.

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Dr. Kodavanti comment (continued): *4) The critical chronic effect; extrathoracic (nasal hyperplasia):* It is not clear how chronic nasal hyperplasia can be related to extra thoracic portal of entry. In my opinion, nasal passages are where the thoracic portal of entry begins.

DPR-HHAB response: The nasal passages are commonly considered to be extrathoracic. A diagram of the human respiratory system with identified extrathoracic, tracheobronchial, and pulmonary regions is found on pages 3-5 of US EPA's position paper on inhalation dosimetry (USEPA, 1994).

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Dr. Kodavanti comment (continued): Nasal epithelium is the first to encounter 1,3-D, and chronic exposure might cause chronic irritation, which leads to hyperplasia of nasal epithelium. It is likely that the translocation of 1,3-D from the nose to the brain can occur through olfactory nerves terminating in the olfactory bulb, which can lead to its detection in other brain regions. However, no brain effects have been studied. If the olfactory neuronal transport of this chemical to the central nervous system is possible, there is a potential for major neuronal effects. Neuronal effects can also occur from respiratory irritation, but no studies have examined this end point. The decreases in body weight might suggest that 1,3-D induces a centrally-mediated systemic stress response. New scientific evidence is rapidly emerging to support such mechanisms in

environmental toxicology. However, the lack of such data for 1,3-D precludes inclusion of such mechanisms in hazard identification.

> **DPR-HHAB response:** Neuronal transport to the brain is a possible mechanism to explain the sensory irritation and perhaps the hyperplastic responses to 1,3-D. However, no support for such a mechanism currently exists.

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Dr. Kodavanti comment (continued): It is stated in the 1997 1,3-D Risk Assessment Document that earlier Telone II formulation contained -1% epichlorohydrin (ECH), which has been shown to be a nasal irritant; however, at this concentration in 1,3-D, it is likely to be below the level that can induce nasal irritation. The cause of observed nasal epithelial, respiratory epithelial and urinary bladder lining epithelium pathology during Telone II inhalation suggests that 1,3-D is also an irritant, and might be linked to sensitization mechanisms. This aspect has not been well studied and not fully discussed in this document.

It is likely that very acute changes in nasal and lung airway epithelial cell injury or inflammation parameters occurred following 1,3-D exposure at much lower concentrations than what has been shown to cause epithelial hyperplasia in the subchronic study. However, in the absence of any studies examining in detail the biological mechanisms, the use of body weight decrements provide the only consistent and usable data set for deriving risk.

> **DPR-HHAB response:** We agree with this assessment.

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Dr. Kodavanti comment (continued): *5) The linearized multistage cancer model and oncogenic effects of 1,3-D:* While the toxicology evidence is clear that chronic exposure to 1,3-D can lead to increased incidence of cancer at the target sites, *i.e.*, upper (nasal) airways and lung in case of inhalation exposure and Gl tissues (stomach , liver) in case of oral gavage, and also at the sites where the metabolites accumulate (urinary bladder), this health concern of 1,3-D supersedes any other non-cancer risk. Since this effect of 1,3-D is most likely through tumor promotion, there is a threshold under which no cancer risk is likely. In the document this conclusion is based on fairly solid earlier toxicology data and the risk estimates are appropriately calculated. The linearized multistage cancer model is used to derive cancer risk, which allows for the estimation of cancer risk at given air concentrations. It is important to derive non-cancer and cancer risk

estimates for different exposure scenarios, but given the fact that 1,3-D exposure can induce tumor promotion, this risk estimate leads to a much lower concentration of 1,3-D which is considered safe, than what will be estimated for non-cancer risk. Appropriate modeling and assumptions are used in deriving cancer risk from exposure to 1,3-D.

> **DPR-HHAB response:** While we are not aware of evidence for inhalation-induced cancer in the upper respiratory tract, Stott et al. demonstrated inhalation-induced adenomas in the bronchioloalveolar region (Stott *et al.*, 1987). It is true that Klaunig argued for a promotional role for 1,3-D in rat livers after oral exposure , though 1,3-D-induced promotion has not been demonstrated in the lung by the inhalation route. The possibility of a threshold mechanism for bronchioloalveolar adenomas, while thoroughly discussed in the Risk Appraisal section, has also not been demonstrated. Finally, while Dr. Kodavanti may be correct that "this risk estimate [as generated by the linearized multistage model] leads to a much lower concentration of 1,3-D which is considered safe, than what will be estimated for non-cancer risk", we feel, as does Dr. Kodavanti, that this was the most appropriate model based on the available data.

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Exposure Assessment

Dr. Kodavanti comment: *1) In several application scenarios, chloropicrin air concentration data are used since no data are available for 1,3-D.* The chloropicrin concentrations used in deriving 1,3-D concentrations were corrected for recovery and the application rate. The exposure estimates, based on chloropicrin data for breathing zone concentrations for each exposure scenario, are derived and then the estimates for each type of exposure were calculated for seasonal, annual and lifetime air concentrations. Although the use of chloropicrin air concentration data is well justified for estimation of 1,3-D concentration, the similarity or differences in volatilization, the molecular weights, the reactivity with soil, and other factors that might influence the ambient levels of each differently is not fully discussed. This information is critical when using chloropicrin data for estimating 1,3-D air concentrations.

> **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, asapplication 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.

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Dr. Kodavanti comment: *2) For estimation of residential bystander exposure, the 1,3-D concentrations downwind at 100 feet distance of the application site, ISCST3 model is appropriately used, which allows for scaling of the air concentration from given application rate to maximum rates.* For simulating air concentrations for 1,3-D, SOFEA2 model was used, but the details about how the volatilization chemistry and soil conditions might be critical and how this model incorporates such factors in estimation of air concentrations is not discussed. It is likely that the model will incorporate these factors in deriving air concentrations of 1,3-D.

DPR-HHAB response: The technical details of SOFEA have undergone extensive review by the US EPA Scientific Advisory Panel (SAP) (USEPA, 2004). Detailed technical description of SOFEA is beyond the scope of the draft 1,3-D RCD but can be found in two articles published by the registrant. (Cryer, 2005; Cryer and van Wesenbeeck, 2011).

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Dr. Kodavanti comment: *3) The human exposure estimates were generated using two scholastic human exposure assessment models; MCABLE and HEESCB.* The differences between these two models in terms of how much volume of data are used by each per simulation and the residential-mobility assumptions employed for estimating exposures are clearly explained. Many individuals reading this document might not be as familiar with the power and accuracy of these models. The information in the document specifically pertaining to these two models regarding different assumptions made in each model, and the instances these models might not predict air concentrations correctly, is not fully explained in the current document.

Annual and lifetime exposure estimates are done using scaling approaches for each exposure scenario and using MCABLE and HEESCB models, which factors in the time of residency in different townships and the mobility times. The scaling for annual and lifetime exposure leads to several fold lower air concentration estimates than episodic high concentration exposures. One time high level exposures are the likely drivers of biological effects.

> **DPR-HHAB response:** We agree with Dr. Kodavanti's comment that detailed discussion on the potential limitations and assumptions employed by HEE5CB and MCABLE are needed. For the latter, the assumptions employed by HEE5CB and MCABLE have been detailed in two separate reports by CDPR (Sanborn and Powell, 1994) and the registrant (Driver *et al.*, 2015), respectively. We have modified the text to indicate that the assumptions employed by these models can be found in the aforementioned reports. With respect to assessing the model limitations, as indicated in the draft 1,3-D RCD, consistency in model outputs suggests that these models can provide a valuable insight into the range of exposures and oncogenic risks associated with the use of 1,3-D in California.
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> Also, we agree with Dr. Kodavanti's comment that "one time high level exposures are the likely drivers of biological effects." A concept similar to Dr. Kodavanti's comment has been also raised by Calabrese and Blain (1999). For 1,3-dichloropropene, the carcinogenic potential associated with a single exposure has yet to be elucidated. Hence, we made no change to the text.

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