Carcinogen Identification Committee (CIC)
Peer Review of the Proposed No Significant Risk Levels (NSRLs) for 1,3-Dichloropropene
Comments by Mariana C. Stern, PhD

SUMMARY: I have reviewed the documents provided by OEHHA, including the Initial Statement of Reasons (ISOR) for the proposal to amend section 25705(B) in Title 27 under Proposition 65, to adopt a No Significant Risk Level (NSRL) for 1,3-dichloropropene. The ISOR prepared is comprehensive and provides all the necessary details to evaluate the process used to arrive to a NSRL threshold for this chemical. Overall, a key concern with this proposed NSRL is that it is based on two studies only, which albeit being of sufficient quality, do not provide sufficient variability to capture potential differences in susceptibility to exposure to this carcinogen. This raises concerns about the potential impact on the human population. The carcinogenesis literature has demonstrated over time that response to chemical carcinogens is highly dependent on strains of mice used, and modalities of exposure and treatment protocols. Therefore, basing this NSRL on two experiments that used the same strain of mice, and only two modalities, raises questions about how well these two experiments can recapitulate the human experience. Specific comments to the suggested questions by OEHHA to guide the review are summarized below. Overall, I think the data is premature to establish a NSRL for 1,3-dichloropropene, and that at a minimum, this decision should merit a discussion with the entire committee to discuss some of these concerns and hear the opinion of various experts.

1. Are the NSRLs based on the most sensitive study, or group of studies, deemed to be of sufficient quality?

This evaluation was based on a two-year gavage study conducted by NTP among B6C3F1 female mice, and a two-year inhalation study among B6C3F1 male mice conducted by Stott *et al.* which were considered to be sensitive studies of sufficient quality. Therefore, this evaluation is based on a very modest number of sensitive and high-quality studies. Ideally, more studies would be valuable to make a more informed decision. In particular, studies that may have used different strains of mice in order to capture potential differences in genetic susceptibility and toxicological response to this chemical, which we know exist in the human population.

2. Is the model selected for dose-response assessment appropriate, based upon the available data for this chemical?

A multistage model was applied to derive cancer potency estimates, and this decision was based on the available mechanistic information, which was summarized by the IARC evaluation in 1999 and the department of Pesticide Regulation (DPR, 2015). It is stated by based on this evidence "there are no principles or assumptions scientifically more appropriate, based on the available data, than this approach". I think this is convincing.

3. Are there available data of such quality that "physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence" that should be used in the assessment?

I did not see in the materials prepared by OEHHA, any existing data on physiology, pharmacokinetics and metabolism that could be considered in this assessment, which is based on two studies. This raises questions about potential differences in susceptibility across different strains of mice, that may recapitulate the existing variability in the human population. Moreover, there are no studies of sufficient quality that could explore the impact on timing of exposure. For example, what would be the consequences in the human population for in-utero exposures?

4. Are the calculations correct (e.g., interspecies scaling of animal to human cancer potency, derivation of NSRLs)?

The calculations for interspecies scaling of animal to human cancer potency, and derivation of NSRLs are correct. However, I have concerns/questions about some of the assumptions made in these calculations and the implications for the human population. In absence of corresponding human epidemiological data, these concerns warrant discussion:

- A dose associated with 5% increased risk of developing tumors was used to calculate the lower bound of the dose using the multistage polynomial model for cancer in the US EPA's Benchmark Dose Software (BMDS). It is not explained why this threshold was chosen. I would have preferred to see corresponding calculations for an even lower threshold to obtain a range of exposures. A 1% increase in risk can translate into large numbers of individuals depending on the incidence rate of a given cancer. For some common cancers, risk factors that increase cancer risk by 1% over the baseline population risk are considered worrisome, as they translate in many excess deaths per year. Some consideration to lower levels needs to be given.

- The interspecies scaling procedure use an average body weight in humans of 70 Kg, which is the assumed value for men according to the risk assessment guidelines used by OEHHA. Given that women can also be exposed to this chemical, calculations should have considered this, as the assumed weight for women is 58, and thus, would result in an even lower threshold for cancer risk increases. The animal experiments do show data for females.

- Similarly, there is concern about the impact this chemical may have on infants, children, and adolescents, where the assumed weighs are even lower, this resulting in even lower thresholds of exposure that could lead to cancer risk increase.

- I have questions about the validity of the interspecies scaling and lifetime dose exposures, considering average lifespan of humans is likely proportionally longer than mice. Therefore, it raises concern about the cumulative effect of exposure to this substance. Also, as mentioned above, there is lack of data to investigate a possible worse effect depending on window of exposure to this chemical. For example, would in utero exposure at the same threshold levels have same low effect as exposure among adults in terms of cancer risk? In absence of those data, it seems it would not be prudent to allow any level of exposure of this chemical in the population.