Office of Environmental Health Hazard Assessment

Lauren Zeise, Ph.D., Acting Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Matthew Rodriquez
Secretary for
Environmental Protection

Edmund G. Brown Jr.
Governor

MEMORANDUM

TO: Marylou N. Verder-Carlos. DVM, MPVM
Assistant Director
Pesticide Programs Division
Department of Pesticide Regulation
1001 I Street
Sacramento, California 95814

FROM: Allan Hirsch
Chief Deputy Director
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, California 95814

DATE: September 20, 2016

SUBJECT: 1,3-DICHLOROPROPENE – OEHHA COMMENTS ON DPR'S DRAFT RISK MANAGEMENT DIRECTIVE (RMD)

On August 30, 2016, the Department of Pesticide Regulation (DPR) provided the Office of Environmental Health Hazard Assessment (OEHHA) with a draft risk management directive (RMD) for 1,3-dichloropropene (1,3-D) that relates to exposures of bystanders (nearby workers and residents) and cancer risk. As stated in Food and Agricultural Code (FAC) Section 14023, DPR is to consult with OEHHA regarding the need for, and appropriate degree of, control measures with regard to pesticides identified as Toxic Air Contaminants (TAC), in this case 1,3-D.

OEHHA's concerns with the draft RMD are explained in detail in the attachment. The draft RMD proposes an annual cap on 1,3-D use of 136,000 adjusted total pounds (ATP) in individual townships, which cover 36 square miles (6 miles by 6 miles) in area.

DPR intends for this cap to achieve a goal of not exceeding a regulatory target concentration of 0.56 parts per billion (ppb) at least 95 percent of the time. OEHHA does not believe that the proposed cap can assure adequate health protection for all residents of a given township. In short, OEHHA's concerns are as follows:

1. The cap was calculated using the annual average air concentration of 1,3-D at one point in a township and ATP of 1,3-D used annually in that 36 square-mile township. The implicit assumption is that 1,3-D use is roughly uniform throughout the township. However, the application of 1,3-D is not uniform; some areas receive more treatment than others and many areas receive none as they are not farmland. Residents who live close to a field treated with higher than the average amount may be exposed to higher air concentrations of 1,3-D than the measured level at the monitor.

2. The calculation is also based on the implicit assumption that annual average air concentration of 1,3-D is roughly uniform throughout a township. However, we know that air contaminants exhibit high spatial variability depending on factors such as proximity to the source, wind direction and velocity, other weather phenomena, and local topography. Residents who live close and downwind from a field treated may be exposed to higher concentrations of 1,3-D than the measured level at the monitor.

3. Furthermore, the use of the proposed township cap to regulate 1,3-D use is also based on the idea that the amount of 1,3-D applied in a 36 square-mile area correlates well with the annual average air concentration of 1,3-D within the township. However, based on past monitoring data and application information presented in the DPR report, OEHHA does not see a correlation between these two parameters; there is not a significant relationship between pounds applied and air concentration. Also of note, a township in Merced received 167,175 ATP of 1,3-D in 2011 (23 percent higher than the proposed cap of 136,000 ATP) and measured an annual average air concentration of 1.92 ppb (more than three-fold higher than the target concentration of 0.56 ppb). Even if 1,3-D use had been at the proposed cap of 136,000 ATP, it appears likely that the annual average air concentration in that township would have well exceeded the target concentration.

4. OEHHA does not agree with DPR's selection of a "portal-of-entry effect" as the preferred Mode of Action for 1,3-D. As explained in the attachment, OEHHA believes the available information supports use of a Mode of Action based on systemic effects, which under DPR's calculations would produce a target air concentration of 0.16 ppb, rather than the proposed concentration of 0.56 ppb.

Additional consideration should be given to the potential for the increased sensitivity of children to carcinogenic effects.

5. Many 1,3-D formulations also contain chloropicrin in significant amounts. Just like 1,3-D, chloropicrin also caused lung cancer in test animals but with a much higher potency. The RMD should address the likelihood that many bystanders exposed to 1,3-D will simultaneously be exposed to chloropicrin.

OEHHA appreciates the opportunity to review and provide consultation on this RMD of 1,3-D. If you have any questions, please contact Dr. David Ting at 510-622-3226.

cc: Lauren Zeise, Ph.D.
Acting Director
Office of Environmental Health Hazard Assessment

David Ting, Ph.D.
Branch Chief
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

Lori Lim, Ph.D., Chief
Pesticide and Food Toxicology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

Charles Salocks, Ph.D., Chief
Pesticide and Epidemiology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

ATTACHMENT

On August 30, 2016, the Department of Pesticide Regulation (DPR) provided the Office of Environmental Health Hazard Assessment (OEHHA) with a draft risk management directive (RMD) for 1,3-dichloropropene (1,3-D) that relates to exposures of bystanders (nearby workers and residents) and cancer risk. As stated in Food and Agricultural Code (FAC) Section 14023, DPR is to consult with OEHHA regarding the need for, and appropriate degree of, control measures with regard to pesticides identified as Toxic Air Contaminants (TAC), in this case 1,3-D.

The RMD cited three supporting documents in determining the regulatory target air concentration and mitigation measures to achieve the target concentration: (a) Rubin, 2016[1], (b) Tao, 2016[2], and (c) Barry and Kwok, 2016[3]. OEHHA requested and received these documents subsequently on September 2, 2016 from DPR. In addition, Rubin (2016) cited a mouse cancer study (Kelly, 1997[4]), which was provided by Dow AgroSciences to DPR in April 2016. OEHHA scientists have not reviewed this study since it was not included in DPR's draft (DPR, 2015a[5]) or final (DPR, 2015b[6]) Risk Characterization Document (RCD) for 1,3-D.

The RMD proposed a regulatory target 1,3-D air concentration of 0.56 parts per billion (ppb) to replace the previous target of 0.14 ppb, and a trigger level of 0.27 ppb. The target concentration is used to calculate the township cap, while the trigger level is

---

[1] Rubin, A. 2016: Memorandum on Response to comments by OEHHA on DPR-HHAB's draft 1,3-dichloropropene risk assessment document, dated August 6, 2016. From Dr. Andrew Rubin to Dr. Shelly DuTeaux, Human Health Assessment Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

[2] Tao, J. 2016: Analysis of Agricultural Use and Average Concentrations of 1,3-Dichloropropene in Nine Communities of California in 2006-2015, and Calculation of a Use Limit (Township Cap). Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

[3] Barry, T. and Kwok, E. 2016: Memorandum on (No December Applications Allowed) Simulation of Cancer Risks Associated with Different Township Cap Scenarios of Merced County for 1,3-Dichloropropene, dated September 2, 2016. From Dr. Terrell Barry and Dr. Eric Kwok to Dr. Shelley DuTeaux, Human Health Assessment Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

[4] Kelly, C.M. 1997. An oncogenicity study with DD-92 in the mouse via oral gavage administration. Huntingdon Life Sciences. East Millstone, NJ. Study #95-2378. DPR Vol. 50046-0240 #291162.

[5] DPR, 2015a. 1,3-Dichloropropene Risk Characterization Document (Draft), August 31, 2015. Human Health Assessment Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. http://cdpr.ca.gov/docs/risk/rcd/dichloro_083115.pdf

[6] DPR, 2015b. 1,3-Dichloropropene Risk Characterization Document, December 31, 2015. Human Health Assessment Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. http://cdpr.ca.gov/docs/risk/rcd/dichloro_123115.pdf

reserved for the evaluation of the mitigation measures. The proposed target value is based on the following:

1. A cancer risk goal of $1x10^{-5}$ for a 70-year lifetime exposure
2. An estimated human cancer potency of 0.018 parts per million $(ppm)^{-1}$ for 1,3-D[7]

The proposed annual township cap is an increase from the current 90,250 adjusted total pounds (ATP) to 136,000 ATP of 1,3-D. The proposed value is based on the following:

1. Yearly average air concentrations of 1,3-D measured by monitoring stations in nine communities in California in 2006-2015.
2. Yearly total 1,3-D use in a township-size area around the air monitoring sites.
3. No application in December, which had some of the highest 1,3-D concentrations[8].
4. The 95th percentile of the paired ratios of yearly average air concentration (in ppb) and yearly ATP of 1,3-D used was estimated to be $4.12x10^{-6}$. Combining this information with the regulatory target air concentration of 0.56 ppb, the township cap of 136,000 ATP was derived[9].

In this attachment, OEHHA's elaborates on comments made in the memorandum regarding the approaches and methods used to derive the proposed regulatory target air concentration and the proposed annual township cap are described below. We provide our input and consultation based on the information obtained for our peer review of the draft RCD as well as that in DPR's three supporting documents mentioned above.

1. <u>The use of the human cancer potency of 0.018 ppm^{-1} and no age sensitivity factor in calculating the target air concentration</u>

In the RMD, DPR chose the portal-of-entry effect over the systemic effect as the preferred mode of action (MOA) for the bronchioalveolar adenomas reported in mice after inhalation exposure (Stott et al., 1987[10]). In OEHHA's review of the draft RCD

---

[7] $1x10^{-5}$ / 0.018 ppm^{-1} = 0.56 ppb
[8] Tao, 2016; Figure 4
[9] 0.56 ppb / $4.12x10^{-6}$ = 135,922 ATP as the township cap
[10] Stott, W.T., Johnson, K.A., Jeffries, T.K., Haut, K.T., and Shabrang, S.N. 1995. Telone II soil fumigant: two-year chronic toxicity/oncogenicity study in Fischer 344 rats. Dow Chemical Company. Laboratory study ID #M-003993-031. DPR Vol. 50046-098 #140562.

(OEHHA, 2015[11]), we recommended that the tumor be considered as a systemic effect since the same type of bronchioalveolar adenoma and carcinoma were found in an oral gavage study in mice (NTP, 1985).

In the RMD and Rubin (2016), DPR justified the portal-of-entry MOA decision by citing: (1) Dow AgroSciences' argument that a stabilizing agent, epichlorohydrin, in the 1,3-D preparation used in the NTP (1985[12]) study was responsible for the lung tumorigenicity and current formulations do not contain epichlorohydrin, and (2) the result of a gavage study (Kelly, 1997) which did not show any increase in lung tumors.

OEHHA agrees with the final RCD (DPR, 2015b), which concluded that the epichlorohydrin in the 1,3-D preparation used in the National Toxicology Program (NTP) study was unlikely to be of sufficient quantities to be responsible for the observed lung tumors.

OEHHA disagrees that results of the Kelly study are sufficient to refute the positive result of the NTP study because there were significant differences in the experimental design of these two oral toxicity studies (Table 1).

Table 1. Differences between the NTP (1985) and Kelly (1997) studies.

	NTP gavage study	**Kelly gavage study**
Mouse strain	$B6C3F_1$, same as in Stott et al inhalation study[13]	CD-1
Duration	2 years (first tumor found on week 78)	18 months (or ~77 weeks)
Doses	Tumors found at 50 and 100 mg/kg-day dose groups	Highest dose tested was 25 mg/kg-day
Dosing regimen	3 times a week on Monday, Wednesday, and Friday	Daily

DPR also calculated the potency and target concentration with systemic effect as the MOA (Rubin, 2016). If the systemic effect MOA had been chosen for the RMD, the

[11] OEHHA, 2015. Document Review: Department of Pesticide Regulation's Draft Risk Characterization Document for 1,3-Dichloropropene. Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. http://oehha.ca.gov/media/downloads/pesticides/report/13-dichloropropenercd-eadmemooehha2015_1.pdf
[12] NTP, 1985. Toxicology and carcinogenesis studies of Telone II in F344/N rats and $B6C3F_1$ mice. NTP Technical Report Series #269.
[13] In the OEHHA comment to DPR's draft RCD (OEHHA, 2015), OEHHA stated in error that they were of different strains.

target air concentration would have been 0.16 ppb, 3.5-fold lower than the 0.56 ppb value.

In addition, in our comments to the draft RCD (OEHHA, 2015), OEHHA recommended that the age sensitivity factor (ASF) to address age-related sensitivity to 1,3-D carcinogenicity be included in the estimation of the human cancer potency factor. The RMD considered the ASF to be unnecessary, but acknowledged that its inclusion would be a health protective goal. It proposed to use an additional uncertainty factor of two to the target concentration and developed a "trigger level" of 0.27 ppb for use in the evaluation of mitigation measures. OEHHA is concerned that such an evaluation would occur only after exposure to the trigger level (or higher) had occurred. Accounting for age sensitivity and portal of entry would reduce the target concentration for mitigation to about 0.1 ppb.

2. The use of paired ratios of yearly average air concentration (in ppb) and yearly ATP of 1,3-D for estimating the township cap

The township cap was based on the ratio of air concentration and usage. The measurements taken at a monitoring station represent air concentrations at a fixed point location, not the entire township of 6x6 miles. Based on the maps presented in Appendices II and III of Tao (2016), some residents are located more than two miles away from the monitoring stations. Also, some residents are very close to the fields where 1,3-D was used in relatively large amounts (e.g., Oxnard in 2012-2015; Salinas in 2011, 2012; Santa Maria in 2014, 2015; Shafter in 2012, 2013); these residents could be exposed to much higher concentrations than those measured at the monitoring stations. When evaluating inhalation exposure, OEHHA recommends consideration of spatial variation of an air contaminant. Depending on local topography, wind direction and velocity, and proximity to the source, air concentrations can vary tremendously even over short distances. It is doubtful that measurements taken at the center of an area of 6x6 miles accurately represent air concentrations at other locations throughout this area.

The RMD used yearly total 1,3-D use in a township-size area to represent usage. OEHHA considers this approach inappropriate because the application is not uniform. Based on the maps presented in Appendices II and III of Tao (2016), it is clear that use of 1,3-D varied enormously within a given township in 2006-2015. The difference in application rate between high- and low-use areas (1x1 mile) was more than 10-fold. In addition, no application was reported in many areas (presumably those are not farmland). This means a large percentage of the "total 1,3-D use" of a township was only applied to a few 1x1 mile areas, and this would be expected to impact the air concentration in the vicinity of these areas more than the township as a whole.

Thus, OEHHA finds uncertainties in the yearly average air concentration and usage determination. For example, the measured concentration of 1.9 parts per billion (ppb) was considerably higher than DPR's 0.56 ppb target concentration for a township with an adjusted use of about 167,000 pounds. Figure 6 in Tao (2016) provided scatterplots of these two variables and found no correlation. In addition, the plots show the slopes to be negative or very shallow. A large increase (300%) in annual 1,3-D ATP application only produced a relatively small increase (approximately 30%) in average yearly concentration. Curiously, the figure also shows the townships with the top two or three measured yearly average concentrations are all associated with relatively low annual 1,3-D usage, below 1×10^5 ATP. Rather than showing a relationship between ATP and air concentration, these results may reflect the proximity of the air monitoring station to nearby application sites.

Not finding a correlation between yearly average air concentration and yearly ATP of 1,3-D usage, Tao (2016) calculated paired ratios of these two variables and found they ranged from less than 0.5×10^{-6} to 6×10^{-6} (Figure 8). The author then selected the 95th percentile of the ratios and used the value, 4.12×10^{-6}, for the calculation of the township cap of 136,000 ATP per year. Due to the issues discussed, OEHHA finds there is a large uncertainty that implementing the township cap of 136,000 ATP per year would achieve the stated goal of reaching the regulatory target concentration of 0.56 ppb at least 95 percent of the time.

3. The proposal to prohibit 1,3-D application in December

OEHHA agrees that there should be no 1,3-D application in periods of calm weather. However, this unfavorable condition may also be present in other months, such as November and January. It would be more health protective to prohibit 1,3-D applications based on meteorological conditions, not the month of the year. Furthermore, we question the approach of removing the December data from the dataset and reallocating it proportionally to the other eleven months of the year.

4. Cancer risk due to co-exposure to 1,3-D and chloropicrin

The RMD should address the likelihood that many bystanders exposed to 1,3-D will simultaneously be exposed to chloropicrin. Based on the data from the 2013 Pesticide Use Report, 1,3-D formulations that contain chloropicrin represent 25% of the 1,3-D pounds applied in California, representing approximately 38% of 1,3-D applications. Carcinogenicity studies in animals suggest that the lung is the target organ for both chemicals and the cancer potency of chloropicrin is much higher than that of 1,3-D.