FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(b) SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

NO SIGNIFICANT RISK LEVELS: 1,3-DICHLOROPROPENE (ORAL AND INHALATION ROUTES)

This is the Final Statement of Reasons for the adoption of No Significant Risk Levels (NSRLs) for 1,3-dichloropropene in Title 27, California Code of Regulations, section 25705(b)[1].

1,3-Dichloropropene was listed as a chemical known to the state to cause cancer for purposes of Proposition 65[2] on January 1, 1989. On October 29, 2021, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt into section 25705(b) NSRLs for 1,3-dichloropropene. The Initial Statement of Reasons (ISOR) that accompanied the Notice of Proposed Rulemaking set forth the grounds for the amendment to the regulation. The NSRLs being adopted are 3.7 micrograms per day (µg/day) for oral and inhalation routes.

SUMMARY

To develop the proposed NSRL for 1,3-dichloropropene by the oral route, OEHHA relied on the 1985 National Toxicology Program (NTP) report entitled “Toxicology and Carcinogenesis Studies of Telone II (Technical-Grade 1,3-Dichloropropene [CAS No. 542-75-6] Containing 1.0% Epichlorohydrin as a Stabilizer) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies)”[3]. To develop the proposed NSRL for 1,3-dichloropropene by the inhalation route, OEHHA relied on inhalation studies of technical grade 1,3-dichloropropene conducted in mice by Stott et al. (1987)[4]. OEHHA also considered and incorporated additional information received from the data call-in period into the

[1] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[2] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq*., hereafter referred to as “Proposition 65” or “The Act”.
[3] National Toxicology Program (NTP, 1985). Toxicology and carcinogenesis studies of Telone II (technical-grade 1,3-dichloropropene [CAS No. 542-75-6] containing 1.0% epichlorohydrin as a stabilizer) in F344/N rats and B6C3F$_1$ mice (gavage studies). TR No. 269. US Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. Available at: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr269.pdf
[4] Stott WT, Johnson KA, Calhoun LL, Weiss SK, Frauson LE (1987). Telone* II soil fumigant: 2-year chronic toxicity-oncogenicity study in mice. Dow Chemical Company. (DPR Vol. 50046-029, Record No. 060675). This set of studies is summarized in Lomax et al. (1989) and DPR (2015).

ISOR. The NSRLs for each route are based upon the results of the most sensitive scientific study deemed to be of sufficient quality[5].

PEER REVIEW

OEHHA provided the Notice of Proposed Rulemaking and the ISOR for the proposed NSRLs for 1,3-dichloropropene to the members of the Carcinogen Identification Committee for their review and comment, as required by Section 25701(e). OEHHA received peer-review comments from committee members Dana Loomis, Ph.D. and Mariana C. Stern, Ph.D.

RESPONSE TO PEER REVIEW COMMENTS RECEIVED

Comment 1 (Dr. Loomis): Dr. Loomis reviewed the ISOR and indicated that the methods used to derive the NSRLs for 1,3-dichloropropene are appropriate and the results appear reasonable.

Response 1: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 2 (Dr. Stern): The ISOR is comprehensive and provides all the necessary details to evaluate the process used to derive the NSRLs.

Response 2: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 3 (Dr. Stern): The two studies that the proposed NSRLs are based on are sensitive and high-quality.

Response 3: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 4 (Dr. Stern): The use of a multistage model to derive cancer potency estimates was appropriate. The calculations for interspecies scaling of animal to human cancer potency, and derivation of NSRLs are correct.

Response 4: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 5 (Dr. Stern): The evaluation was based on two studies. Ideally, more studies would be valuable to make a more informed decision, such as studies using different strains of mice in order to capture potential differences in genetic susceptibility and toxicological response to this chemical.

[5] Section 25703(a)(4)

Response 5: NSRLs are based on the most sensitive studies of sufficient quality available at the time of development, following the criteria, principles and assumptions specified in Section 25703. As discussed in the ISOR, a number of rodent cancer bioassays of 1,3-dichloropropene have been conducted, using multiple strains of mice and rats (see Table 1 of the ISOR). OEHHA identified the inhalation study in male B6C3F1 mice by Stott et al. 1987[6] and the oral gavage study in female B6C3F1 mice by NTP[7] as being the most sensitive scientific studies of sufficient quality to meet the criterion in Section 25703. These studies were therefore chosen for the derivation of the NSRLs.

No changes to the proposed regulation were made based on this comment.

Comment 6 (Dr. Stern): Overall, the data are premature to establish an 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.

Response 6: 1,3-Dichloropropene has a relatively large dataset of animal cancer bioassays, which includes several studies of sufficient quality, including an NTP report presenting the results from studies in male and female mice and rats. OEHHA developed the NSRLs based on scientifically appropriate methods following the guidance set forth in Section 25703. The methods used to derive the NSRLs are consistent with standard methodology used by OEHHA[8], as well as US EPA[9].

Members of the Carcinogen Identification Committee provide peer review on proposed NSRLs in accordance with Section 25701(e), which specifies that whenever OEHHA proposes to adopt "a level of exposure to a listed carcinogen that shall be deemed to pose no significant risk of cancer, the lead agency shall provide to each member of the Carcinogen Identification Committee notice of the proposed action, the proposed change to the regulation, and a copy of the initial statement of reasons supporting the proposal for their review and comment."[10] OEHHA followed the process outlined in regulation, which does not include a requirement for the Carcinogen Identification Committee to meet.

No changes to the proposed regulation were made based on this comment.

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[6] Stott et al. (1987), full citation provided in footnote 4.
[7] NTP (1985), full citation provided in footnote 3.
[8] OEHHA (2009). Air Toxics Hot Spots Risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors" (May 2009), Office of Environmental Health Hazard Assessment. Available at: http://www.oehha.ca.gov/air/hot_spots/tsd052909.html
[9] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.
[10] Section 25701(e)

Comment 7 (Dr. Stern): Data on physiology, pharmacokinetics, and metabolism were not in the materials prepared by OEHHA. 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?

Response 7: OEHHA followed procedures established in Section 25703, which address uncertainties when direct data are not available, consistent with standard risk assessment practice and consistent with advice by scientific authorities[11]. Some recent illustrative studies relating to pharmacokinetics were provided in the ISOR (e.g., Bartels et al. 2020[12]), but an exhaustive list of studies on the pharmacokinetics and metabolism of 1,3-dichloropropene was not included. OEHHA reviewed the available studies and did not consider the available pharmacokinetic data sufficient to support an alternative approach to cancer potency estimation and followed the procedures laid out in regulation in Section 25703. Regarding *in utero* exposure, unfortunately, no studies in animals with *in utero* exposure were identified in the literature that met the criterion in Section 25703 as being sensitive studies of sufficient quality.

No changes to the proposed regulation were made based on this comment.

Comment 8 (Dr. Stern): No reason for using a dose associated with a 5% increased risk of developing tumors to calculate the lower bound of the dose in BMDS was given. Corresponding calculations for a lower threshold, such 1%, would have been preferred. 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.

Response 8: OEHHA agrees that a 1% increase in risk can translate into large numbers of individuals depending on the incidence rate of a given cancer. The NSRL reflects a risk level of 1/100,000 (10^{-5}), not 1%. In order to estimate the animal cancer slope factor (CSF_{animal} or animal cancer potency) we use US EPA's Benchmark Dose Software (BMDS)[13]. Use of the BMDS entails estimating the dose associated with a particular benchmark response. For modeling tumor incidence data from animal cancer bioassays, OEHHA typically uses a benchmark response level of 5%. The animal

[11] National Research Council (2009). Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press. Available at: https://doi.org/10.17226/12209.

[12] Bartels MJ, Hackett MJ, Himmelstein MW, Green JW, Walker C, Terry C, Rasoulpour R, Challender M, Yan ZJ (2020). Metabolic basis for nonlinearity in 1,3-dichloropropene toxicokinetics and use in setting a kinetically-derived maximum inhalation exposure concentration in mice. Toxicol Sci 174:16-24.

[13] US EPA Benchmark Dose Software (BMDS). National Center for Environmental Assessment, US EPA. Available at: https://www.epa.gov/bmds.

cancer slope factor (CSF_{animal}) is calculated as the ratio of the dose associated with a 5% increased risk of developing a tumor to the lower bound (estimated using the multistage polynomial model for cancer in US EPA's BMDS) for this dose. The CSF_{animal} is converted to a CSF_{human}, which is used to derive the NSRL. The NSRL is defined as the daily intake that would result in 1/100,000 (10^{-5}) cancer risk over a lifetime of exposure.

Choosing a benchmark response level of 5% is a science policy practice that is generally health protective. OEHHA's standard procedure is to use a benchmark response level of 5% unless there is a reason to use a different response level. In this case, changing from a 5% to a 1% response level does not, in fact, substantially alter the CSF_{animal} or CSF_{human} estimates. Specifically, for the multisite analysis of tumors in female mice, the CSF_{animal} was 0.0268 $(mg/kg\text{-}day)^{-1}$ using a benchmark response of 5%, and 0.0273 $(mg/kg\text{-}day)^{-1}$ using a benchmark response of 1%. Both estimates of CSF_{animal} result in a CSF_{human} of 0.19 $(mg/kg\text{-}day)^{-1}$. For the multisite analysis of tumors in male mice, the CSF_{animal} was 0.0279 $(mg/kg\text{-}day)^{-1}$ using a benchmark response of 5% and 0.0285 $(mg/kg\text{-}day)^{-1}$ using a benchmark response of 1%. These CSF_{animal} values result in estimates of CSF_{human} of 0.19 $(mg/kg\text{-}day)^{-1}$ and 0.20 $(mg/kg\text{-}day)^{-1}$, when rounded to two significant figures, respectively.

Thus, the choice between a 5% or 1% benchmark response level typically results in negligible or no change to the NSRL, as in this case.

No changes to the proposed regulation were made based on this comment.

Comment 9 (Dr. Stern): The interspecies scaling procedure uses an average body weight in humans of 70 kg. Calculations should consider lower weights for women, infants, children, and adolescents.

Response 9: OEHHA applied the default approaches in Section 25703 to convert from an estimate of cancer potency in animals to a human cancer potency estimate and NSRLs that apply to the general population. The approach uses representative body weights in humans and the species on which the potency is based. The use of 70 kg as a default body weight is taken as representative of the human population and is intended to protect the entire general population. This body weight is specified in Section 25703(a)(8). The use of a lower human body weight in the interspecies scaling calculation from animals to humans would not result in a lower NSRL.

No changes to the proposed regulation were made based on this comment.

Comment 10 (Dr. Stern): There are questions about the validity of the interspecies scaling and the animal lifetime dose exposures (e.g., two years taken as 'lifetime' for mice), and whether they adequately account for the cumulative effect of exposure in the human population, as well as *in utero* exposure.

Response 10: As specified in Sections 25701 and 25703, OEHHA uses standard quantitative cancer risk assessment methodologies, principles, and assumptions to derive human cancer slope factors (potencies) applicable to the general human population (see also OEHHA, 2009[14]). When deriving cancer slope factors from carcinogenesis studies conducted in mice and rats, an exposure duration of two years is generally accepted to be equivalent to lifetime exposure for purposes of carcinogenicity testing[15]. The interspecies scaling procedure, where the animal cancer slope factor (CSF_{animal}) is extrapolated to a human cancer slope factor (CSF_{human}), is specified in Section 25703(a)(6) and consists of multiplying the CSF_{animal} by a scaling factor equivalent to the ratio of human to animal body weight, taken to the one-fourth power. As discussed in the response to comment 9, a human body weight value of 70 kg is used in scaling the CSF_{animal} to the CSF_{human} value.

As specified in Section 25703(b), the Proposition 65 no-significant-risk value is defined as one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question. The NSRL is the daily intake that would result in that level of cancer risk over a lifetime. As discussed in the response to comment 9, the NSRLs for 1,3-dichloropropene apply to the general population.

No changes to the proposed regulation were made based on this comment.

PUBLIC COMMENTS

A public comment period was provided from October 29, 2021 to December 13, 2021. The notice stated that a public hearing would be held upon request. No request for a public hearing was received. OEHHA received written public comments on the proposed rulemaking from the following organizations:

- Combined comments from eight individuals (Sellen et al.)
- Combined comments from Californians for Pesticide Reform, Safe Ag Safe Schools, California Rural Legal Assistance Foundation, Californians for Alternatives to Toxics, Central California Asthma Collaborative, Santa Cruz for Bernie, Pesticide Action Network, Sonoma Safe Ag Safe Schools, Clean Water Action, Michael Freund & Associates, Center for Biological Diversity, Physicians for Social Responsibility, Center on Race, Poverty and the Environment, Families Advocating for Chemical and Toxics Safety, Center for Environmental Health, Valley Improvement Projects, Physicians for Social Responsibility, CAUSE, Central California Environmental Justice Network, Monterey Bay Central Labor Council, Central Valley Air Quality Coalition,

[14] OEHHA (2009), full citation provided in footnote 8.
[15] Gold LS, Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

Ventura County Coalition Advocating for Pesticide Safety, and Tulare County Coalition Advocating for Pesticide Safety (CPR et al.)

- Center for Environmental Health (CEH)
- Dow Chemical Company (Dow)
    - These comments also contained two attachments comprised of a letter to CalEPA Secretary Jared Blumenfeld and the comments previously submitted to OEHHA by Dow during the 2021 request for information relevant to the development of an NSRL for 1,3-dichloropropene. OEHHA considered these comments during the development of the NSRLs and incorporated additional information received during the data call-in period into the ISOR.

RESPONSE TO PUBLIC COMMENTS

A summary of the relevant public comments received and OEHHA's responses are provided in this FSOR. Some comments did not constitute an objection to or recommendation directed at the regulatory proposal for which comments were solicited or the procedures followed in this rulemaking process. Consistent with the Administrative Procedure Act, OEHHA is not required to respond to such comments in the FSOR. The absence of responses to such comments should not be construed to mean that OEHHA in any way agrees with or disagrees with them.

Comment 11 (CEH, Sellen et al., CPR et al.): Three commenters support the proposed NSRLs and find that the levels were derived using appropriate methods and assumptions and are consistent with Proposition 65 and the implementing regulations.

Response 11: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 12 (CEH, CPR et al.): Exposure to 1,3-dichloropropene in California is widespread and at times exceeds DPR's regulatory target in towns such as Shafter and Parlier. The proposed NSRL will achieve a more health-protective regulatory limit. The majority of 1,3-dichloropropene is used in ZIP code areas with more Latinx/Hispanic residents than the California average, making 1,3-dichloropropene exposure an environmental justice issue.

Response 12: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 13 (CEH): CEH supports OEHHA's use of a multisite approach to estimate the cancer potency of 1,3-dichloropropene due to the evidence of systemic effects from inhalation and oral exposure to this carcinogen. Studies have found statistically significant increases in the incidence of tumors in multiple sites following inhalation or oral exposure to 1,3-dichloropropene in mice and rats. The evidence presented by these studies is consistent with the choice of a systemic mode of action.

Response 13: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 14 (Sellen et al., CPR et al.):

Sellen et al. stated:

"The NSRL is based on tumor frequency at two sites: the lungs and the lacrimal glands. Combining tumor from multiple sites to estimate cancer potency is recommended by several authoritative agencies. The U.S. Environmental Protection Agency cancer guidelines state that tumors at multiple sites strengthen the evidence for carcinogenicity of a substance, and that risk estimates from different tumor sites should be added.[1] The National Research Council also supports this approach.[2] [footnote references found in comment] OEHHA has used tumors at multiple sites to calculate cancer potency and NSRLs at least ten times in the last two decades (p-chloroaniline, p-chloroanilinehydrochloride, chlorothalonil, dibenzo[a,i]pyrene, dibromoacetic acid, diisononyl phthalate, glycidol, s-methylchrysene, nitromethane, and tris(1,3-dichloro-2-propyl) phosphate)."

CPR et al. stated:

"In particular, we support the use of what is called the "multisite" approach to estimating cancer potency. This approach is health-protective, consistent with the relevant regulations, and has been used by OEHHA at least a dozen times in the last two decades to set safe harbor levels.".

Response 14: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 15 (Sellen et al.): "The NSRL is based on cancer potency calculated from the frequency of the combination of adenomas and carcinomas. Summing adenomas and carcinomas is supported by the World Health Organization (International Agency for Research on Cancer)[3] and the U.S. Environmental Protection Agency[1] when scientifically appropriate. OEHHA has used a combination of adenomas and carcinomas to calculate cancer potency at least nine times in the last two decades (p-chloroaniline, p-chloroaniline hydrochloride, chlorothalonil, p-chloro-α,α,α-trifluorotoluene, dibromoacetic acid, diisononyl phthalate (DINP), glycidol, nitromethane, tris(1,3-dichloro-2-propyl) phosphate)."

Response 15: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 16 (Sellen et al.): "Tumor frequencies in unexposed (control) animals from the study used to calculate cancer potency are consistent with historical control values. Charles River states that the historical control values for the strain of mice used in the 1,3-dichloropropene cancer study are 0.5% (range 0 – 7.0%) for lacrimal gland

cystadenomas, 8.3% (range 0 - 24.6% for bronchiolar/alveolar adenomas, and 1.9% (range 0 - 5.8%) for bronchiolar/alveolar carcinoma.[4] Control frequencies in the 1,3-dichloropropene study were 2% for lacrimal gland tumors and 18% for bronchiolar/alveolar tumors. In addition, in both cases, frequencies in the animals exposed to the highest doses of 1,3-dichloropropene (12% for lacrimal gland tumors and 44% for bronchiolar/alveolar tumors) were above the historical control range."

Response 16: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 17 (Dow): "Because OEHHA's proposal is not a response to a need for greater clarity among the regulated community but instead an effort to support the goals of activists seeking to influence ongoing regulatory proceedings and court proceedings, and for the other reasons stated below, Dow opposes OEHHA's proposal."

"Dow is the sole manufacturer of products containing 1,3-D, and every package of 1,3-D sold or distributed for use in California bears an appropriate Proposition 65 warning for cancer. No business has requested that OEHHA issue a regulatory default NSRL for 1,3-D, and indeed every major trade association representing businesses who use 1,3-D in California has urged OEHHA not to proceed to establish such a regulatory default NSRL."

"It is virtually unprecedented for OEHHA to proceed to establish a regulatory default level for a chemical in the face of concreted opposition from the business community that is intended to be the beneficiary of the clarity provided by such a level, and there is no reason for OEHHA to deviate from its past practice here."

"For the reasons explained above and in the exhibits, OEHHA should abandon this effort to assist activist groups and withdraw its October 29, 2021 proposal. In the alternative, OEHHA should acknowledge the validity of the data and analysis submitted by Dow in its May 25, 2021 response to OEHHA's request for information."

"Should OEHHA proceed to adopt a regulatory default NSRL for 1,3-D, it should emphasize the limited effect of that regulation, as it has in other rulemakings, namely that it is 'solely for purposes of' Proposition 65 and cannot 'be construed to establish or exposure or risk levels for other regulatory purposes.' 27 Cal. Code Regs. § 25701(d). And that it does not 'preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in [the OEHHA regulations] to establish that a level of exposure to a listed chemical poses no significant risk.' 27 Cal. Code Regs. § 25701(a)."

Response 17: On April 15, 2019, OEHHA was petitioned by Californians for Pesticide Reform requesting a rulemaking pursuant to Government Code §11340.6 to adopt an NSRL for 1,3-dichloropropene. On February 24, 2021, OEHHA formally granted the Petition. In the response to the petition, OEHHA explained that a No Significant Risk

Level for this chemical could be useful to the enforcement and business community. OEHHA's grant of the petition does not reflect OEHHA's agreement with or endorsement of any particular statements included in the petition.[16] On March 12, 2021, OEHHA issued a request for scientific information relevant to the development of an NSRL for 1,3-dichloropropene. At the request of the Dow Chemical Company, on April 9, 2021 OEHHA extended the data call-in period to close on May 26, 2021.

OEHHA develops NSRLs to provide "safe harbors" from Proposition 65 warning requirements if exposure to a chemical occurs at or below these levels. All regulatory NSRLs adopted by OEHHA are non-mandatory guidance levels businesses can use. However, nothing prohibits a business from calculating an alternative, higher NSRL that it would need to defend in court if challenged (Sections 25701 and 25703).

Additionally, as the lead state entity responsible for the implementation of Proposition 65[17], OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[18]. OEHHA develops and adopts NSRLs to provide guidance for determining when a warning is required for exposures to chemicals listed under Proposition 65 as causing cancer. NSRLs are adopted into regulation in Title 27, California Code of Regulations, Section 25705, which is specific to Proposition 65.

OEHHA thoroughly and carefully considered all material submitted by Dow in response to the request for information, including their recommendation to set an NSRL of 50 µg/day or higher. For detailed response on the alternative of 50 µg/day, see response 20 and the ISOR.

No changes to the proposed regulation were made based on this comment.

Comment 18 (Dow): "OEHHA proposed to establish a regulatory default NSRL for 1,3-D by two routes of exposure: inhalation and oral. But 1,3-D was listed by the State's Qualified Experts on the basis of gavage (oral exposure) data only. The State's Experts specifically excluded inhalation as the basis for listing. Therefore, it would be inappropriate to develop a regulatory default NSRL for exposures by inhalation because the inhalation pathway is not relevant under Proposition 65. *See* The Dow Chemical Company Response to Request for Information Relevant to the Development of an NSRL for 1,3-D (May 25, 2021) (Exhibit 2), at pp. 2-4. [2] [footnote reference found in comment] Dow has previously commented on this issue, and OEHHA has dismissed its

[16] OEHHA (2021). Response to Petition for Rulemaking Setting a No Significant Risk Level for 1,3-Dichloropropene. February 24, 2021. Available at: https://oehha.ca.gov/media/downloads/crnr/responseltrtopetition3122021.pdf

[17] Section 25102(o).
[18] Health and Safety Code, section 25249.12(a).

comments summarily and refused its request for a meeting to discuss this issue. Dow therefore reiterates its comments here in hopes that OEHHA will consider them."

Response 18: The issue of inhalation exposure was addressed in the ISOR. As explained in the ISOR, the listing for 1,3-dichloropropene[19] is not limited with respect to route of exposure, there is no qualifier specifying a route of exposure. Thus, it is not appropriate to exclude studies in which animals were exposed via inhalation in developing the NSRL(s). Furthermore, 1,3-dichloropropene induces tumors in animals when administered via inhalation, gavage, and diet. It would not be scientifically justifiable to ignore sensitive studies of sufficient quality in which tumors were observed based on the route or pathway of administration.

No changes to the proposed regulation were made based on this comment.

Comment 19 (Dow): "In arriving at its proposed regulatory default NSRL of 3.7 micrograms per day, OEHHA made multiple conservative assumptions, some of which are quite controversial and novel in the scientific community, and compounded these with faulty methodology."

Dow listed several methods and assumptions used in the ISOR, which are summarized here as comments 22, 23, 24, and 25.

Response 19: OEHHA used scientifically appropriate methods and followed the guidance set forth in Section 25703. These are standard procedures for cancer dose-response analysis that are followed by OEHHA[20] and other risk assessment agencies. Comments about specific methods and assumptions are addressed in the responses to comments 20, 21, 22, and 23.

No changes to the proposed regulation were made based on this comment.

Comment 20 (Dow): "DPR's scientific evaluation of the data concluded that a portal-of-entry approach was appropriate; that approach would lead to an NSRL of 50 micrograms per day."

"As discussed above, scientists at the California Department of Pesticide Regulation, who have assessed 1,3-D in multiple contexts and immersed themselves for years in the data on this chemical, believe it is most appropriately assessed using the portal-of-entry approach. DPR's 2015 1,3-Dichloropropene Risk Characterization Document ("RCD") emphatically states that the weight of the evidence supports 1,3-D as a portal-

[19] Section 27001. Chemicals Known to the State to Cause Cancer or Reproductive Toxicity. Available at: https://govt.westlaw.com/calregs/Document/I54B9D2B0D45011DEA95CA4428EC25FA0?viewType=FullText&originationContext=documenttoc&transitionType=StatuteNavigator&contextData=%28sc.Default%29&bhcp=1

[20] OEHHA (2009), full citation provided in footnote 8.

of-entry carcinogen. OEHHA's use of a systemic approach accounts for more than a 3-fold difference in the default regulatory NSRL."

"In the alternative, OEHHA should acknowledge the validity of the data and analysis submitted by Dow in its May 25, 2021 response to OEHHA's request for information. Based on that data and analysis, OEHHA should adopt a regulatory default NSRL for 1,3-D of at least 50 micrograms/day."

Response 20: As discussed in the ISOR, OEHHA reviewed the large number of available rodent carcinogenicity studies of 1,3-dichloropropene (see Table 1 of the ISOR) and selected the most sensitive scientific studies deemed to be of sufficient quality for dose-response analyses and NSRL development. Following the guidance in Section 25703, OEHHA developed NSRLs of 3.7 µg/day for the oral and inhalation routes.

As explained in the ISOR, DPR in fact "chose to characterize lung tumorigenesis in both ways because the data did not point overwhelmingly to one or the other scenario, though we felt ultimately that the evidence tilted to the portal of entry scenario"[21]. Both portal-of-entry and systemic exposures may result in lung tumors in mice. Lacrimal gland tumors were also observed in male mice exposed via inhalation in the same study (Stott et al. 1987[22]), which a portal-of-entry scenario cannot explain. Thus, a systemic exposure scenario is more likely for the lacrimal gland tumors. In conducting the dose-response analysis of the tumor data from Stott et al. inhalation study in male mice[23], OEHHA determined that it would be most scientifically appropriate to treat 1,3-dichloropropene as a systemic carcinogen.

Thus, OEHHA disagrees with the commenter, and finds it would not be scientifically appropriate to set an NSRL of 50 µg/day or higher.

No changes to the proposed regulation were made based on this comment.

Comment 21 (Dow): "In its risk assessment of 1,3-D, DPR based its inhalation cancer slope factor on the most sensitive tumor type in an animal study, which was lung bronchioloalveolar adenoma and carcinoma in male mice in the Stott et al. (1987) study. In contrast, OEHHA based its human inhalation cancer slope factor on multiple tumor sites, including bronchioloalveolar adenomas and carcinomas, as well as lacrimal gland cystadenoma and carcinoma in male mice in the Stott et al. (1987) study. OEHHA did a similar analysis on oral exposure data. In essence, OEHHA 'added up' the cancer slope

[21] Department of Pesticide Regulation (DPR, 2015). 1,3-Dichloropropene risk characterization document: inhalation exposure to workers, occupational and residential bystanders and the general public. Human Health Assessment Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.
[22] Stott et al. (1987), full citation provided in footnote 4.
[23] *Ibid.*

factors for any tumors that it considered positive. This accounts for more than a 2-fold difference in the default regulatory NSRL."

Response 21: OEHHA conducted multisite analyses but did not "add up" the cancer slope factors. US EPA's Benchmark Dose Software[24] has a multi-site model that is used to estimate a cumulative risk of carcinogen treatment-related tumors by summing the maximum likelihood estimates for the individual multistage models for the different cancer sites for each study. It is OEHHA's longstanding practice to conduct multisite analyses, and, as noted in comment 14 above, US EPA and the National Research Council support the use of multisite approaches to estimate cancer potency in studies where tumors are induced at multiple sites. US EPA's benchmark dose training module for cancer models[25] explains, "Basing unit risk estimates on only one tumor type may underestimate the carcinogenic potential of a chemical that is observed to induce neoplasia at multiple sites in a bioassay (NRC, 1994)."[26] The National Research Council states, "In the analysis of animal bioassay data on the occurrence of multiple tumor types, the cancer potencies should be estimated for each relevant tumor type that is related to exposure, and the individual potencies should be summed for those tumors."[27] Therefore, OEHHA appropriately conducted multisite analyses for the male and female mouse studies of 1,3-dichloropropene since multiple treatment-related tumor types were observed in each study.

No changes to the proposed regulation were made based on this comment.

Comment 22 (Dow): "In developing the NSRLs for 1,3-D, OEHHA did not use the tumor incidences reported by Stott et al. (1987) and NTP (1985). Instead, OEHHA obtained the raw data and expressed the cancer data as the number of mice with tumors in the numerator and the number of mice alive at the appearance of the first tumor in the denominator. Usually, the denominator is the number of animals assigned to the study, not the number alive at the appearance of the first tumor. The lower the denominator, the higher the incidence of tumors and therefore the higher the cancer slope factor."

Response 22: The effective tumor incidence is the number of tumor-bearing animals (numerator) over the number of animals alive at the time of first occurrence of the tumor (denominator). This method of tallying tumor incidence removes animals from the assessment that died before they are considered at risk for tumor development. The use of the effective number is a standard practice employed by US EPA and OEHHA in

[24] US EPA BMDS, full citation provided in footnote 13.
[25] US EPA (2014). Benchmark Dose Modeling – Cancer Models. Benchmark Dose Software Training Webinars. Available at: https://clu-in.org/conf/tio/bmds/slides/BMDS_Cancer_Models.pdf
[26] *Ibid*.
[27] National Research Council (1994). Science and Judgment in Risk Assessment. Washington, DC: The National Academies Press. Available at: http://www.nap.edu/catalog/2125.html

evaluating tumor incidence findings from animal cancer bioassays (assuming that the study reported individual animal data on both time of death and tumor findings). US EPA commonly reports tumor incidences as the number of tumor-bearing animals over the number of animals examined, excluding those that died or were sacrificed before observation of the first tumor or before a particular week of the study. For example, US EPA's evaluation of iprodione reported tumor incidences as the "# of tumor-bearing rats/# of rats examined, excluding those that died or were sacrificed before observation of the first tumor"[28], and the US EPA's evaluation of CMNP reported tumor incidences as "Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53"[29]. OEHHA's standard practice is to use effective numbers for cancer hazard identification (for example, C.I. Disperse Yellow 3[30]), as well as for cancer dose-response assessment (for example, vinylidene chloride[31], hexavalent chromium[32], and tertiary-butyl acetate[33]) when the necessary data are available. In the event that significant differences in survival between treated and control groups are observed, e.g., differential early mortality, a poly-3 adjustment to tumor incidence expressed as effective number (or alternatively, a time-to-tumor model) may be selected for use in dose-response analyses. The poly-3 method calculates a survival-adjusted rate that "accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice"[34].

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[28] US EPA (1994). Carcinogenicity Peer Review of Iprodione. Health Effects Division, Office of Prevention, Pesticides, and Toxic Substances. See p. 5.
[29] US EPA (2011). Cancer Assessment Document. Evaluation of the carcinogenic potential of CMNP (Pyrazachlor) PC Code 207100. Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs, September 20. See p. 10.
[30] OEHHA (2012). Evidence on the carcinogenicity of C.I. Disperse Yellow 3. Reproductive and Cancer Hazard Assessment Branch, OEHHA, California Environmental Protection Agency, August. See pp. 10, 12. Available at: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/081012ciyhid.pdf.
[31] OEHHA (2017). Initial Statement of Reasons. Title 27, California Code of Regulations, Proposed Amendment to Section 25705(b) Specific Regulatory Levels Posing No Significant Risk: Vinylidene Chloride. See p. 3. Available at: https://oehha.ca.gov/media/downloads/crnr/isorvinylidenechloride092217.pdf.
[32] OEHHA (2011). Public Health Goals for Chemicals in Drinking Water: Hexavalent Chromium (Cr VI). Pesticide and Environmental Toxicology Branch, OEHHA, California Environmental Protection Agency, July. See p. 51. Available at: https://oehha.ca.gov/media/downloads/water/chemicals/phg/cr6phg072911.pdf.
[33] OEHHA (2018). Air Toxics Hot Spots Program *Tertiary*-Butyl Acetate Cancer Inhalation Unit Risk Factor, Technical Support Document for Cancer Potency Factors. Appendix B. Air and Site Assessment and Climate Indicator Branch, OEHHA, California Environmental Protection Agency, August. See p. 50. Available at: https://oehha.ca.gov/media/downloads/crnr/tbaccanceriur081018.pdf.
[34] National Toxicology Program (NTP, 2009). Toxicology and Carcinogenesis Studies of Bromochloroacetic Acid (CAS No. 5589-96-8) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NTP Technical Report Series No. 549. NIH Publication No. 09-5890. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Thus, OEHHA's use of effective number in reporting tumor incidence is well justified, and consistent with the practices of other authoritative bodies, including US EPA and NTP, that also take into account early deaths in assessing tumor data from animal studies.

No changes to the proposed regulation were made based on this comment.

Comment 23 (Dow): "OEHHA used the linear multistage model in determining its proposed regulatory default NSRL. As noted in Dow's May 25, 2021 Response to Request for Information (at p. 5), in 2019 the U.S. Environmental Protection Agency, which regulates 1,3-D under the Federal Insecticide, Fungicide, and Rodenticide Act, recommended using a threshold-based point of departure for all forms of chronic toxicity (including cancer) associated with exposure to 1,3-D. EPA implemented this approach in its 2020 Registration Review of 1,3-D."

Response 23: OEHHA does not agree that a threshold approach is appropriate for the dose-response assessment of 1,3-dichloropropene. As described in the ISOR, consideration of the available mechanistic information on 1,3-dichloropropene, including evidence of genotoxicity, supports an assumption of linearity in the dose-response at low doses and indicate that the most appropriate method for calculating a cancer potency is the multistage model.

No changes to the proposed regulation were made based on this comment.

Alternatives Determination

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. Six suggested alternatives were suggested during the data call-in period and these alternatives were carefully considered and discussed in the ISOR. No additional alternatives have been suggested. OEHHA has determined that no reasonable alternative would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses "no significant risk" of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to establish No Significant Risk Levels for 1,3-dichloropropene. At or below this level, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting this level will allow businesses subject to the Act to determine whether a given discharge to sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25349.6).

Although Section 25703 describes principles and assumptions for conducting risk assessments to derive No Significant Risk Levels, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting an NSRL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

Local Mandate Determination

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts, nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.