INITIAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

PROPOSED AMENDMENT TO:
SECTION 25705(B) SPECIFIC REGULATORY LEVELS
POSING NO SIGNIFICANT RISK

1,3-DICHLOROPROPENE (ORAL AND INHALATION ROUTES)

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986
PROPOSITION 65

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENT

This proposed regulatory amendment would adopt No Significant Risk Levels (NSRLs) for 1,3-dichloropropene under Proposition 65[1] in Title 27, California Code of Regulations, section 25705(b)[2]. The proposed NSRLs of 3.7 micrograms per day (µg/day) for the oral and inhalation routes for 1,3-dichloropropene are based on carcinogenicity studies of 1,3-dichloropropene in rodents and were derived using the methods described in Section 25703.

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to adopt and amend regulations to implement and further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals into sources of drinking water. Warnings

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et. seq., commonly known as Proposition 65, hereafter referred to as “Proposition 65” or “the Act”.
[2] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[3] Section 25102(o).
[4] Health and Safety Code, section 25249.12(a).

are not required and the discharge prohibition does not apply when exposures are insignificant. NSRLs provide guidance for determining when a warning is required for exposures to chemicals listed as causing cancer.

1,3-Dichloropropene was listed as known to the state to cause cancer under Proposition 65 on January 1, 1989. In April 2019 OEHHA received a Petition from Californians for Pesticide Reform requesting that OEHHA adopt a safe harbor NSRL for 1,3-dichloropropene. 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, OEHHA extended the data call-in period to May 26, 2021.

DEVELOPMENT OF PROPOSED NSRLS

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)"[5]. 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)[6]. OEHHA also considered and incorporated additional information received from the data call-in period into this Initial Statement of Reasons.

Tables listing the data extracted from Stott et al. (1987) and relied on by OEHHA are included here as Appendix A. These studies are available from the California Department of Pesticide Regulation (DPR) upon completing a confidentiality agreement regarding use of the studies, as required by Government Code section 6254.2(h)[7]. OEHHA also relied on a publication by Lomax et al. (1989) entitled "The Chronic Toxicity and Oncogenicity of Inhaled Technical-Grade 1,3-Dichloropropene in Rats and

[5] 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 from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr269.pdf

[6] 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).

[7] https://www.cdpr.ca.gov/docs/registration/affirmstat2.pdf

Mice"[8], which presented information from the Stott et al. (1987)[9] mouse inhalation studies.

Volume 71 in the series of International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, entitled "Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide"[10], the 2015 Risk Characterization Document from DPR[11], and seven publications[12,13,14,15,16,17,18] provide additional information on genotoxicity.

The NSRLs for 1,3-dichloropropene are based upon the results of the most sensitive scientific studies deemed to be of sufficient quality[19].

[8] Lomax LG, Stott WT, Johnson KA, Calhoun LL, Yano BL, Quast JF (1989). The chronic toxicity and oncogenicity of inhaled technical-grade 1,3-dichloropropene in rats and mice. *Fundamental and Applied Toxicology* 12:418-31.
[9] Stott et al. (1987), full citation provided in footnote 6.
[10] International Agency for Research on Cancer (IARC, 1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC, World Health Organization, Lyon, France. Available from: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-50/
[11] 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.
[12] Creedy CL, Brooks TM, Dean BJ, Hutson DH, Wright AS (1984). The protective action of glutathione on the microbial mutagenicity of the Z-and E-isomers of 1,3-dichloropropene. *Chem Biol Interact* 50:39-48.
[13] Watson WP, Brooks TM, Huckle KR, Hutson DH, Lang KL, Smith RJ, Wright AS (1987). Microbial mutagenicity studies with (Z)-1,3-dichloropropene. *Chem Biol Interact* 61:17-30.
[14] Neudecker T and Henschler D (1986). Mutagenicity of chloroolefins in the Salmonella/mammalian microsome test. III. Metabolic activation of the allylic chloropropenes allyl chloride, 1,3-dichloropropene, 2,3-dichloro-1-propene, 1,2,3trichloropropene, 1,1,2,3-tetrachloro-2-propene and hexachloropropene by S9 mix via two different metabolic pathways. *Mutat Res* 170:1-9.
[15] Neudecker T, Stefani A, Henschler D (1977). *In vitro* mutagenicity of soil nematocide 1,3-dichloropropene. *Experientia (Basel)* 33: 1084-1085.
[16] Neudecker T, Lutz D, Eder E, Henschler D (1980). Structure-activity relationship in halogen and alkyl substituted allyl and allylic compounds: correlation of alkating and mutagenic properties. *Biochem Pharmacol* 29:2611-2617.
[17] Eder E, Henschler D, Neudecker T (1982). Mutagenic properties of allylic and a,b-unsaturated compounds: Consideration of alkylating mechanisms. *Xenobiotica* 12: 831-848.
[18] Badding M, Gollapudi BB, Gehen S, Yan Z (2020). In vivo mutagenicity evaluation of the soil fumigant 1,3-dichloropropene. *Mutagenesis* 35:437-443.
[19] Section 25703(a)(4).

Selection of Studies Used to Determine Cancer Potency

OEHHA identified 16 rodent carcinogenicity studies in eight publications or reports[20,21,22,23,24,25,26,27] of 1,3-dichloropropene through a systematic search of the published scientific literature and technical reports submitted to or prepared by government agencies (Table 1). Default rodent body weights were obtained from Gold and Zeiger (1997)[28] and used by OEHHA in calculating lifetime average doses for some of these studies.

[20] Stott et al. (1987), full citation provided in footnote 6.
[21] Lomax et al. (1989), full citation provided in footnote 8.
[22] NTP (1985), full citation provided in footnote 5.
[23] Kelly CM (1997). An oncogenicity study with DD-92 in the mouse via oral administration. American Cyanamid Company and Huntingdon Life Sciences. Information from this set of studies is summarized in Appendix B.
[24] Stebbins KE, Johnson KA, Jeffries TK, Redmond JM, Haut KT, Shabrang SN, Stott WT (2000). Chronic toxicity and oncogenicity studies of ingested 1,3-dichloropropene in rats and mice. *Regulatory Toxicology and Pharmacology* 32:1-13.
[25] Lomax LG, Calhoun LL, Stott WT, Frauson LE (1987). Telone II soil fumigant: 2-year inhalation chronic toxicity-oncogenicity study in rats. (DPR Vol. No. 50046-0031, Record No. 060677). This set of studies is summarized in Lomax et al. (1989) and DPR (2015).
[26] Kelly CM (1998). A chronic toxicity and oncogenicity study with DD-92 in the rat via oral administration. American Cyanamid Company and Huntingdon Life Sciences. Information from this set of studies is summarized in Appendix B.
[27] Stott WT, Johnson KA, Jeffries TK, Haut KT, Shabrang SN (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. No. 50046-098, Record No. 140562). This set of studies is summarized in Stebbins et al. (2000) and DPR (2015).
[28] Gold LS and Zeiger E (1997). Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Inc., Boca Raton.

Table 1. Overview of rodent carcinogenicity studies of 1,3-dichloropropene

Sex, strain	Route of administration	Duration (months)	Doses (mg/kg-d)	Test material	Treatment-related tumor findings	Reference[a]
Mice						
Male, B6C3F1	Inhalation, 6 hr/d, 5 d/wk	24	0, 4.8, 19.1, 57.5[b]	Telone II[c]	Lung adenoma or carcinoma; lacrimal gland cystadenoma or carcinoma	Stott et al. (1987); Lomax et al. (1989)*
Female, B6C3F1	Inhalation, 6 hr/d, 5 d/wk	24	0, 5.6, 22.4, 67.0[d]	Telone II[c]	None reported	Stott et al. (1987); Lomax et al. (1989)
Male, B6C3F1	Gavage, 3 times/wk	24	0, 19.1, 38.1[b]	Telone II[e]	Lung adenoma or carcinoma; hepatocellular adenoma or carcinoma	NTP (1985)
Female, B6C3F1	Gavage, 3 times/wk	24	0, 19.1, 38.1[b]	Telone II[e]	Urinary bladder transitional cell carcinoma; lung adenoma; forestomach squamous cell papilloma or carcinoma	NTP (1985)*
Male, CD-1	Gavage, once/d, 7 d/wk	18	0, 2, 10, 25[f]	DD-92[g]	None reported	Kelly (1997)
Female, CD-1	Gavage, once/d, 7 d/wk	18	0, 2, 10, 25[f]	DD-92[g]	Bladder submucosal mesenchymal tumor	Kelly (1997)
Male, B6C3F1	Diet	24	0, 2.5, 25, 50[f]	Microencapsules in feed[h]	None reported	Stebbins et al. (2000)
Female, B6C3F1	Diet	24	0, 2.5, 25, 50[f]	Microencapsules in feed[h]	None reported	Stebbins et al. (2000)
Rats						
Male, F344	Inhalation, 6 hr/d, 5 d/wk	24	0, 3.6, 14.3, 43.0[d]	Telone II[c]	None reported	Lomax et al. (1987); Lomax et al. (1989)
Female, F344	Inhalation, 6 hr/d, 5 d/wk	24	0, 4.0, 16.2, 48.4[d]	Telone II[c]	None reported	Lomax et al. (1987); Lomax et al. (1989)
Male, F344	Diet	24	0, 2.5, 12.7, 25.4[f]	Microencapsules in feed[h]	Hepatocellular adenoma	Stott et al. (1995); Stebbins et al. (2000)

Sex, strain	Route of administration	Duration (months)	Doses (mg/kg-d)	Test material	Treatment-related tumor findings	Reference[a]
Female, F344	Diet	24	0, 2.5, 12.7, 24.8[f]	Microencapsules in feed[h]	Hepatocellular adenoma	Stott et al. (1995); Stebbins et al. (2000)
Male, F344/N	Gavage, 3 times/wk	24	0, 9.5, 19.1[b]	Telone II[e]	Forestomach squamous cell papilloma or carcinoma; liver adenoma; adrenal gland pheochromocytoma	NTP (1985)
Female, F344/N	Gavage, 3 times/wk	24	0, 9.5, 19.1[b]	Telone II[e]	Mammary gland fibroadenoma	NTP (1985)
Male, Sprague-Dawley CD	Gavage, once/d, 7 d/wk	23	0, 2, 10, 25[f]	DD-92[g]	None reported	Kelly (1998)
Female, Sprague-Dawley CD	Gavage, once/d, 7 d/wk	24	0, 2, 10, 25[f]	DD-92[g]	None reported	Kelly (1998)

[a] Complete references appear in text footnotes 20–27

[b] Doses calculated by OEHHA using body weight reported by study authors

[c] 92.1% 1,3-dichloropropene; 0.7% 1,2-dichloropropane; 1.8% 1,3-dichloropropane; 1.1% 1-chlorohexane; remainder mixed isomers of chlorohexane, chlorohexene, and trichloropropene. Epoxidized soybean oil (2%) added as a stabilizing agent

[d] Doses calculated by OEHHA using default body weights following Gold and Zeiger (1997), full citation provided in footnote 27.

[e] Approximately 89% cis- and trans-1,3-dichloropropene; 2.5% 1,2-dichloropropane; 1.5% trichloropropene isomer; 1.0% epichlorohydrin (added as a stabilizer)

[f] Doses reported by study authors

[g] DD-92, in liquid form, was supplied by the American Cyanamid Company. 94.8% purity. “Dosages were adjusted to correct for purity” (Kelly 1997, 1998)

[h] 1,3-Dichloropropene, obtained from Dow AgroSciences, LLC, as Telone II soil fumigant, was microencapsulated in a starch/sucrose matrix (80/20%). 1,3-Dichloropropene was stabilized with approximately 2% epoxidized soybean oil. The liquid 1,3-dichloropropene was determined to have a chemical purity of 96.0 +/- 0.2% (50.7 +/- 0.6% cis; 45.1 +/- 0.5% trans)

*Determined to be sensitive studies of sufficient quality

OEHHA reviewed the available data from the rodent carcinogenicity studies and determined that the two-year gavage study conducted by NTP[29] in female B6C3F$_1$ mice and the two-year inhalation study in male B6C3F$_1$ mice reported by Stott et al. (1987)[30] and Lomax et al. (1989)[31] met the criterion in Section 25703 as being sensitive studies of sufficient quality. Other studies in which tumors were observed were determined to be less sensitive than these studies.

The two-year gavage study conducted by NTP[32] in female B6C3F$_1$ mice is considered a sensitive study of sufficient quality. Groups of 50 female mice were exposed to technical grade 1,3-dichloropropene (Telone II) via gavage at concentrations of 0, 50, or 100 milligrams per kilogram of body weight (mg/kg) three times per week for 104 weeks. The chemical composition of the test material was determined to be 88-90% 1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% trichloropropene isomer, 1% epichlorohydrin, and some other impurities. OEHHA examined the issues related to the presence of epichlorohydrin and 1,2-dichloropropane and concluded that they could not have substantially affected the 1,3-dichloropropene cancer potency estimate (see p. 14 for a more detailed discussion). In order to account for the purity of the test material and the dosing schedule, OEHHA calculated lifetime average daily doses (see pp. 12-14 for calculations). The lifetime average daily doses of 1,3-dichloropropene resulting from administration of the test material[33] in the female mouse study were calculated to be 0, 19.1, and 38.1 mg/kg-day for the control, low-dose, and high-dose groups, respectively. Survival was significantly lower in the high-dose group than in the controls, with a statistically significant trend[34].

In the NTP female mouse oral study[35], statistically significant increases in the incidence of urinary bladder transitional cell carcinoma were observed in the low- and high-dose groups, with a statistically significant positive trend. Statistically significant increases in alveolar/bronchiolar adenoma and forestomach squamous cell papilloma or carcinoma (combined) were observed in high-dose females, with statistically significant positive trends. A statistically significant increase in hepatocellular adenoma or carcinoma (combined) was observed in the low-dose group; however, these tumors were not

[29] NTP (1985), full citation provided in footnote 5.
[30] Stott et al. (1987), full citation provided in footnote 6.
[31] Lomax et al. (1989), full citation provided in footnote 8.
[32] NTP (1985), full citation provided in footnote 5.
[33] In calculating the lifetime average daily dose, the test material was taken to be 89% 1,3-dichloropropene.
[34] NTP (1985), full citation provided in footnote 5.
[35] *Ibid.*

increased in the high-dose group ($p > 0.2$), and a dose-related trend was not observed ($p > 0.2$). The tumor incidence data used to estimate cancer potency for the oral route from this study are presented in Table 2.

Table 2. Tumor incidences[a] of treatment-related lesions in female B6C3F$_1$ mice administered 1,3-dichloropropene by gavage (NTP, 1985)

Organ	Tumor type	1,3-Dichloropropene administered doses (mg/kg of body weight)[b]			Trend test *p*-value[c]
		0	44.5	89	
Urinary bladder	Transitional cell carcinoma[d] (first occurrence of tumor: day 525)	0/49	8/49**	21/40***	$p < 0.001$
Lung	Alveolar/bronchiolar adenoma[d] (first occurrence of tumor: day 490)	0/50	3/50	8/43**	$p < 0.001$
Forestomach	Squamous cell papilloma or carcinoma[d] (first occurrence of tumor: day 651)	0/48	1/48	4/40*	$p < 0.05$

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
[b] The administered dose for Telone II was 0, 50, and 100 mg/kg of body weight. NTP (1985) reported that the Telone II preparation was 88-90% 1,3-dichloropropene. OEHHA used 89% purity for calculating the administered dose of 1,3-dichloropropene.
[c] *p*-values for exact trend test conducted by OEHHA.
[d] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In the inhalation study in male mice reported by Stott et al. (1987)[36] and Lomax et al. (1989)[37], groups of 50 male mice were exposed to 1,3-dichloropropene via inhalation of vapors of Telone II soil fumigant (whole-body chamber) at concentrations of 0, 5, 20, or 60 ppm (corresponding to 0, 22.7, 90.8, and 272.4 mg/m^3, respectively) for 6 hours/day, 5 days/week for up to 24 months. The chemical composition of the test material was determined to be 92.1% 1,3-dichloropropene, 0.7% 1,2-dichloropropane, 1.8% 1,3-dichloropropane, 1.1% 1-chlorohexane, and some other impurities. Epoxidized soybean oil (2%) was added as a stabilizing agent. The lifetime average daily doses of

[36] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[37] Lomax et al. (1989), full citation provided in footnote 8.

1,3-dichloropropene in the study were calculated to be: 0, 4.8, 19.1, and 57.5 mg/kg-day in male mice. Survival of male mice was not affected by treatment at any dose.

In this inhalation study in male mice[38,39], a statistically significant increase in the incidence of bronchioloalveolar adenoma or adenocarcinoma (combined) was observed in the high-dose group, with a statistically significant positive trend. Statistically significant increases in lacrimal gland cystadenoma and carcinoma (combined) were observed in the low- and mid-dose groups. The tumor incidence data used to estimate cancer potency for the inhalation route from this study are presented in Table 3.

Table 3. Tumor incidences[a] of treatment-related lesions in male B6C3F$_1$ mice administered 1,3-dichloropropene by inhalation (Stott et al. 1987, Lomax et al. 1989, and Appendix A)

Organ	Tumor type	1,3-Dichloropropene administered concentrations (mg/m^3)[b]				Trend test *p*-value[c]
		0	20.9	83.6	251	
Lung	Bronchioloalveolar adenoma or adenocarcinoma[d, e] (first occurrence of tumor: day 558)	9/49	6/49	13/49	22/50**	$p < 0.001$
Lacrimal gland	Cystadenoma or carcinoma[d] (first occurrence of tumor: day 590)	1/49	7/49*	10/49**	6/49	NS

[a] The numerator represents the number of tumor-bearing animals and the denominator represents the number of animals alive at the time of first occurrence of tumor.
[b] The administered dose for Telone II was 0, 22.7, 90.8, and 272 mg/m^3. Stott et al. (1987) reported that these concentrations of Telone II soil fumigant, containing 92.1% 1,3-dichloropropene, correspond to doses of 1,3-dichloropropene of approximately 0, 20.9, 83.6, and 251 mg/m^3, respectively.
[c] *p*-values for exact trend test conducted by OEHHA. NS, not significant.
[d] Treatment group tumor incidences with asterisks indicate significant results from Fisher pairwise comparison with controls (performed by OEHHA): * $p < 0.05$, ** $p < 0.01$
[e] There was one mouse in the mid-dose group with an adenoma and an adenocarcinoma (animal No. 84A0477).

Estimation of Cancer Potency Using the Multistage Model

Studies on the genotoxicity of 1,3-dichloropropene have been reviewed and summarized in DPR's Risk Characterization Document[40] and the 1999 IARC

[38] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[39] Lomax et al. (1989), full citation provided in footnote 8.
[40] DPR (2015), full citation provided in footnote 11.

Monograph[41]. These studies were conducted in a variety of *in vitro* and *in vivo* systems, with and without metabolic activation, and several without the presence of impurities such as epichlorohydrin.

In mammalian test systems, 1,3-dichloropropene induced chromosomal aberrations in bone marrow in male B6C3F1 mice *in vivo* and micronucleated polychromatic erythrocytes in male B6C3F1 mice and female NMRI mice *in vivo*. It did not induce micronuclei formation in male NMRI or CD-1 mice or female CD-1 mice or increase the incidence of dominant lethal mutations in male Crl:CD(SD) rats[42]. 1,3-Dichloropropene induced DNA damage in cells isolated from organs of male and female Sprague-Dawley rats exposed via intraperitoneal injection or gavage in several assays[43]. It did not induce mutations at the *lacI* transgene in lung and liver tissue isolated from male Big Blue B6C3F1 mice exposed to 1,3-dichloropropene via inhalation[44,45]. As discussed in DPR's Risk Characterization Document[46], this Big Blue mouse study had several limitations, including inadequate exposure duration and an insufficient high dose; thus, it may not have been able to detect an effect. In male Big Blue F344 rats exposed to 1,3-dichloropropene via the diet, no mutations were observed at the *cII* transgene in liver or kidney tissues[47].

In *in vitro* systems, 1,3-dichloropropene induced sister chromatid exchanges, but not chromosomal aberrations, in Chinese hamster ovary cells with and without metabolic activation[48]. In cultured hamster lung V79 cells and cultured rat hepatocytes, 1,3-dichloropropene induced DNA single-strand breaks[49]. In non-mammalian test systems, 1,3-dichloropropene was mutagenic in *Salmonella typhimurium*, with and without metabolic activation[50,51]. Several of these tests showing genotoxic effects were

[41] IARC (1999), full citation provided in footnote 10.
[42] DPR (2015), full citation provided in footnote 11.
[43] *Ibid*.
[44] *Ibid.*
[45] Badding et al. (2020), full citation provided in footnote 18.
[46] DPR (2015), full citation provided in footnote 11.
[47] Badding et al. (2020), full citation provided in footnote 18.
[48] DPR (2015), full citation provided in footnote 11.
[49] *Ibid.*
[50] DPR (2015), full citation provided in footnote 11.
[51] IARC (1999), full citation provided in footnote 10.

conducted with individual isomers or with purified test material[52,53,54,55,56,57]. 1,3-Dichloropropene also induced sex-linked recessive lethal mutations in *Drosophila melanogaster*[58].

In addition, several metabolites of 1,3-dichloropropene are also genotoxic, including 3-chloro-2-hydroxypropanal and 3-chloroacrolein[59].

In reviewing the genotoxicity of 1,3-dichloropropene, DPR's Risk Characterization Document concluded that 1,3-dichloropropene is considered genotoxic, stating "[c]ollectively, these studies provide convincing evidence that 1,3-D, its oxidative metabolites and autoxidation products have genotoxic potential"[60].

In its Summary of Data Reported and Evaluation, the 1999 IARC Monograph[61] stated the following:

> "1,3-Dichloropropene induces micronuclei in the bone marrow of female mice, as well as sister chromatid exchanges and DNA damage in cultured mammalian cells. It is mutagenic to bacteria."

Based on consideration of the available mechanistic information on 1,3-dichloropropene, a multistage model is applied to derive a cancer potency estimate. For purposes of this NSRL and following the guidance in Section 25703, there are no principles or assumptions scientifically more appropriate, based on the available data, than this approach.

The lifetime probability of a tumor at a specific site given exposure to the chemical at dose d is modeled using the multistage polynomial model:

$$p(d) = \beta_0 + (1 - \beta_0)\left(1 - \exp\left[-\left(\beta_1 d + \beta_2 d^2 + \cdots + \beta_j d^j\right)\right]\right)$$

[52] Creedy et al. (1984), full citation provided in footnote 12.
[53] Watson et al. (1987), full citation provided in footnote 13.
[54] Neudecker and Henschler (1986), full citation provided in footnote 14.
[55] Neudecker et al. (1977), full citation provided in footnote 15.
[56] Neudecker et al. (1980), full citation provided in footnote 16.
[57] Eder et al. (1982) full citation provided in footnote 17.
[58] DPR (2015), full citation provided in footnote 11.
[59] *Ibid*.
[60] *Ibid*.
[61] IARC (1999), full citation provided in footnote 10.

where the background probability of tumor, β_0, is between 0 and 1 and the coefficients β_i, i = 1…j, are positive. The β_i are parameters of the model, which are taken to be constants and are estimated from the data. The parameter β_0 provides the basis for estimating the background lifetime probability of the tumor.

To derive a measure of the cancer response to 1,3-dichloropropene (per mg/kg-day) in the studies described above, the dose associated with a 5% increased risk of developing a tumor was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in US EPA's Benchmark Dose Software (BMDS)[62]. The multistage model is the default approach to modeling lifetime cancer bioassay data, as stated in US EPA's 2005 cancer risk assessment guidelines[63]. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, US EPA's BMDS[64] can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models for the different sites and/or cell types. This multisite model provides a basis for estimating the cumulative risk of carcinogen treatment-related tumors. In order to derive a measure of the total cancer response in a given study, the dose associated with a 5% increased risk of developing a tumor at one or more of the sites of interest was calculated and the lower bound for this dose was estimated using the multisite model in BMDS. The ratio of the 5% risk level to that lower bound on dose is known as the multisite "animal cancer slope factor (CSF_{animal})," or "animal cancer potency." Animal cancer potencies were estimated using this approach for the female mouse gavage study described in Table 2 and the male mouse inhalation study described in Table 3.

Calculation of Average Daily Doses

The lifetime average dose in units of mg/kg-day of 1,3-dichloropropene was calculated for each of the relevant dose groups, based on the reported purity of the technical grade 1,3-dichloropropene used, and the dose level, duration, exposure regimen, and animal body weights reported by NTP[65] for the oral route study and Stott et al. (1987)[66] and

[62] US EPA Benchmark Dose Software (BMDS) Version 2.7.0.4. National Center for Environmental Assessment, US EPA. Available from: https://www.epa.gov/bmds.
[63] US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.
[64] *Ibid.*
[65] NTP (1985), full citation provided in footnote 5.
[66] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.

Lomax et al. (1989)[67] for the inhalation route study. The average body weight for female mice in the oral study was calculated to be 0.0306 kg from the data reported by NTP[68] for control animals. The average body weight for male mice in the inhalation study was calculated to be 0.0312 kg from the data reported by Stott et al. (1987)[69] for control animals.

For the oral study in female mice, OEHHA adjusted for the purity of 1,3-dichloropropene in Telone II (approximately 89%, as reported by NTP 1985) in calculating the administered dose of 1,3-dichloropropene (see Table 2). Mice were dosed via oral gavage three days per week for 104 weeks at 0, 25, or 50 mg/kg of body weight. The equation for lifetime average dose (D_{avg}, in mg/kg-day) calculation for dosing via gavage is:

$$D_{avg}\ (\text{mg/kg-day}) = \text{Gavage dose}\left(^{\text{mg}}/_{\text{kg}}\right) \times \frac{3\ \text{doses/week}}{7\ \text{days/week}}$$

Thus, the lifetime average doses were calculated to be 19.1 and 38.1 mg/kg-day for the low- and high-dose groups in the NTP (1985) study.

For the inhalation study in male mice, OEHHA adjusted for the purity of 1,3-dicloropropene in Telone II (92%, as reported by Stott et al. 1987) in calculating the administered dose of 1,3-dichloropropene (see Table 3). The inhalation rate (IR), in m^3/day for the male mice was calculated based on the equations of Anderson et al. (1983)[70], which were derived using experimental data on animal breathing rates (m^3/day) and corresponding body weights (kg):

$$IR_{mice} = 0.0345 \times (bw_{mice}/0.025)^{2/3}$$

The constant 0.0345 is in m^3/day and the constant 0.025 is in kg. The calculated inhalation rate was 0.040 m^3/day for male mice in this study. D_{avg} were determined by multiplying the chamber air concentration (C_{air}) of 1,3-dichloropropene in units of mg/m^3 by the following factors: the inhalation rate divided by the body weight; 6/24 to account for the 6 hours per day exposure; 5/7 to account for a five day per week dosing

[67] Lomax et al. (1989), full citation provided in footnote 8.
[68] NTP (1985), full citation provided in footnote 5.
[69] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[70] Anderson EL and the Carcinogen Assessment Group of the US EPA (1983). Quantitative approaches in use to assess cancer risk. *Risk Analysis* 3:277-295.

regimen. The equation for lifetime average dose (mg/kg-day) calculation for the male mice is:

$$D_{avg} = C_{air}\left(\frac{mg}{m^3}\right) \times \frac{IR_{mice}}{bw_{mice}} \frac{\left(\frac{m^3}{day}\right)}{kg} \times \frac{6}{24} \times \frac{5}{7}$$

Thus, the lifetime average doses were calculated to be 4.8, 19.1, and 57.5 mg/kg-day for the low-, mid-, and high-dose groups in the inhalation study in male mice[71,72].

Potential Effects of Epichlorohydrin and 1,2-Dichloropropane on Estimation of Cancer Potency

In the NTP oral gavage study in female mice, the test material Telone II contained 1% epichlorohydrin and 2.5% 1,2-dichloropropane, two carcinogens listed under Proposition 65. In the Stott et al. (1987) inhalation study in male mice, the test material Telone II contained 0.7% 1,2-dichloropropane. NTP (1985) considered the potential influencing effects of 1,2-dichloropropane and epichlorohydrin in the oral gavage studies, and concluded that "the 2.5% 1,2-dichloropropane in the Telone II® preparation was not considered to be responsible for any of the toxic response", and that epichlorohydrin "may have a role in the chronic toxicity (including carcinogenicity) in the present studies". OEHHA examined these issues and reached similar conclusions regarding the potential effects of 1,2-dichloropropane and epichlorohydrin in these studies. In addition, OEHHA concluded that the presence of epichlorohydrin in the NTP oral gavage study may have contributed to a small extent to the tumors observed in the forestomach, but not to the incidence of tumors observed at other sites. Based on estimates of site-specific cancer potencies (i.e., based solely on forestomach tumor responses) calculated for 1,3-dichloropropene in the oral NTP study, and for epichlorohydrin from epichlorohydrin carcinogenicity studies, the presence of epichlorohydrin at 1% in the NTP test material could not have substantially affected the 1,3-dichoropropene cancer potency estimate.

Estimation of Human Cancer Potency

Human cancer potency is estimated by an interspecies scaling procedure. According to Section 25703(a)(6), dose in units of mg per kg body weight scaled to the three-quarters

[71] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[72] Lomax et al. (1989), full citation provided in footnote 8.

power is assumed to produce the same degree of effect in different species in the absence of information indicating otherwise. Thus, for each of the studies described above, scaling to the estimated human potency (CSF_{human}) is achieved by multiplying the animal potency (CSF_{animal}) by the ratio of human to animal body weights (bw_{human}/bw_{animal}) raised to the one-fourth power when CSF_{animal} is expressed in units $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = CSF_{animal} \times (bw_{human} / bw_{animal})^{1/4}$$

The default human body weight is 70 kg. The average body weights for male and female mice were calculated to be 0.0312 kg and 0.0306 kg, respectively, based on the data reported for control animals by Stott et al. (1987)[73] for the male mouse study and by NTP (1985)[74] for the female mouse study. The derivations of the human cancer slope factors using these body weights are summarized below in Table 4.

[73] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[74] NTP (1985), full citation provided in footnote 5.

Table 4. Derivation of CSF_{human} using mean animal body weights for the studies and data presented in Tables 2 and 3

Sex/strain/species	Type of neoplasm	Body Weight (kg)	CSF_{animal} $(mg/kg\text{-}day)^{-1}$	CSF_{human} $(mg/kg\text{-}day)^{-1}$
Female $B6C3F_1$ mice (oral study)	Urinary bladder transitional cell carcinoma	0.0306	0.0195	
	Lung alveolar/bronchiolar adenoma		0.00705	
	Forestomach squamous cell papilloma or carcinoma		0.00399	
	Multisite**:** bladder transitional cell carcinoma; alveolar/bronchiolar adenoma; forestomach squamous cell papilloma or carcinoma		0.0268	**0.19**
Male $B6C3F_1$ mice (inhalation study)	Lung bronchioloalveolar adenoma or adenocarcinoma	0.0312	0.0108	
	Lacrimal gland cystadenoma or carcinoma[a]		0.0202	
	Multisite: bronchioloalveloar adenoma or adenocarcinoma; lacrimal gland cystadenoma or carcinoma		0.0279	**0.19**

[a] The top dose group had to be removed during the modeling process to achieve sufficient goodness of fit.

The NSRL via the oral route for 1,3-dichloropropene will be based on the multisite human cancer slope factor of 0.19 $(mg/kg\text{-}day)^{-1}$, derived from the NTP oral study in female mice[75].

The NSRL via the inhalation route for 1,3-dichloropropene will be based on the multisite human cancer slope factor of 0.19 $(mg/kg\text{-}day)^{-1}$, derived from the inhalation study in male mice reported by Stott et al. (1987)[76] and Lomax et al. (1989)[77].

Calculation of No Significant Risk Levels

The NSRL can be calculated from the cancer slope factor as follows. The Proposition 65 no-significant-risk value is one excess case of cancer per 100,000 people exposed,

[75] NTP (1985), full citation provided in footnote 5.
[76] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[77] Lomax et al. (1989), full citation provided in footnote 8.

expressed as 10^{-5}. This value is divided by the slope factor, expressed in units of one divided by milligram per kilogram body weight per day. The result of the calculation is a dose level associated with a 10^{-5} risk in units of mg/kg-day. This dose then can be converted to an intake amount in units of mg per day by multiplying by the body weight for humans. When the calculation is for the general population, the body weight is assumed to be 70 kg[78]. The intake can be converted to a µg per day amount by multiplying by 1000. This sequence of calculations can be expressed mathematically as:

$$\text{NSRL} = \frac{10^{-5} \times 70\ \text{kg}}{\text{CSF}_{\text{human}}} \times 1000\ \mu\text{g/mg}.$$

As indicated previously, the human cancer slope factor for 1,3-dichloropropene via the oral route derived from the female mouse study data and exposure parameters presented in Table 2 is 0.19 per mg/kg-day. Inserting this number into the equation above results in an NSRL for 1,3-dichloropropene via the oral route of 3.7 µg/day.

The human cancer slope factor for 1,3-dichloropropene via the inhalation route derived from the male mouse study data and exposure parameters presented in Table 3 is 0.19 per mg/kg-day. Inserting this number into the equation above results in an NSRL for 1,3-dichloropropene via the inhalation route of 3.7 µg/day.

Thus the NSRL is 3.7 µg/day for both the inhalation and oral routes. When exposure occurs via both inhalation and oral routes, the NSRL is 3.7 µg/day for the combined exposure from the two routes.

PROPOSED REGULATORY AMENDMENT

Section 25705(b)

The proposed change to Section 25705(b) is provided below, in underline.

> (1) The following levels based on risk assessments conducted or reviewed by the lead agency shall be deemed to pose no significant risk:

[78] Section 25703(a)(8).

Chemical name	Level (micrograms per day)
Acrylonitrile	0.7
…	
1,3-Dichloropropene	3.7 (oral) 3.7 (inhalation)
…	

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the resources and expertise to examine the scientific literature and calculate a level of exposure, in this case an NSRL, that does not require a warning or for which a discharge is not prohibited.

ECONOMIC IMPACT ASSESSMENT (see below)

NECESSITY

This proposed regulatory amendment would adopt NSRLs that conform with the Proposition 65 implementing regulations and reflect the currently available scientific knowledge about 1,3-dichloropropene. The NSRLs provide assurance to the regulated community that exposures or discharges at or below these levels are considered not to pose a significant risk of cancer. Exposures at or below the NSRLs are exempt from the warning and discharge requirements of Proposition 65[79].

BENEFITS OF THE PROPOSED REGULATION

See “Benefits of the Proposed Regulation” under ECONOMIC IMPACT ANALYSIS below.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

The following documents were relied on by OEHHA for calculating the oral and inhalation NSRLs for 1,3-dichloropropene.

[79] Health and Safety Code sections 25249.9(b) and 25249.10(c).

- The 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)"[80].
- The report of Stott et al. (1987) entitled "Telone II soil fumigant: two-year chronic toxicity/oncogenicity study in mice"[81], and the publication by Lomax et al. (1989) entitled "The Chronic Toxicity and Oncogenicity of Inhaled Technical-Grade 1,3-Dichloropropene in Rats and Mice"[82].
- The 1999 IARC Monograph on 1,3-dichloropropene[83].
- The DPR 1,3-dichloropropene risk characterization document[84].
- The publications by Anderson et al. (1983)[85] and Gold and Zeiger (1997)[86].
- Publications on genotoxicity[87,88,89,90,91,92,93].

The IARC Monograph, the DPR document, and the publications by Creedy et al. (1984), Watson et al. (1987), Neudecker and Henschler (1986), Neudecker et al. (1977; 1980), Eder et al. (1982), and Badding et al. (2020) provide additional information on genotoxicity. Copies of these documents will be included in the regulatory record for this proposed action. These documents are available from OEHHA upon request.

OEHHA also relied on the following Economic Impact Analysis, included in this document, in developing this proposed regulation.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

The NSRLs provide "safe harbor" values that aid businesses in determining if they are

[80] NTP (1985), full citation provided in footnote 5.
[81] Stott et al. (1987), full citation provided in footnote 6. See also tables listing the data extracted from Stott et al. (1987) in Appendix A.
[82] Lomax et al. (1989), full citation provided in footnote 8.
[83] IARC (1999), full citation provided in footnote 10.
[84] DPR (2015), full citation provided in footnote 11.
[85] Anderson et al. (1983), full citation provided in footnote 70.
[86] Gold and Zeiger (1997), full citation provided in footnote 28.
[87] Creedy et al. (1984), full citation provided in footnote 12.
[88] Watson et al. (1987), full citation provided in footnote 13.
[89] Neudecker and Henschler (1986), full citation provided in footnote 14.
[90] Neudecker et al. (1977), full citation provided in footnote 15.
[91] Neudecker et al. (1980), full citation provided in footnote 16.
[92] Eder et al. (1982), full citation provided in footnote 17.
[93] Badding et al. (2020), full citation provided in footnote 18.

complying with the law. One alternative to the proposed amendment to Section 25705(b) would be to not adopt NSRLs for this chemical. Failure to adopt these NSRLs would leave the business community without "safe harbor" levels to assist businesses in complying with Proposition 65.

Additionally, commenters responding to OEHHA's request for scientific information relevant to the development of an NSRL for 1,3-dichloropropene suggested alternatives to the proposed regulation. Brief descriptions of the suggested alternatives and OEHHA's reasons for rejecting these alternatives are presented below.

Alternative 1: An NSRL is not needed because the tumor findings for 1,3-dichloropropene are limited

Several commenters state that the tumor findings for 1,3-dichloropropene in rodent carcinogenicity studies are "limited". OEHHA disagrees that the tumor findings are limited. In fact, there are robust tumor data for 1,3-dichloropropene, including the observations of urinary bladder, lung, and forestomach tumors in the study in female mice by NTP[94], and lung and lacrimal gland tumors in the study in male mice by Stott et al. (1987)[95] (see Tables 2 and 3). Commenters also stated that newer studies found that 1,3-dichloropropene is not as carcinogenic as was observed in the NTP (1985) studies conducted in male and female mice and rats. However, the fact that some studies did not observe tumors or observed few tumors reflects differences in study design, such as differences in dosing, strain of animal, or length of study. It does not provide evidence that 1,3-dichloropropene is not carcinogenic.

Dow also commented that OEHHA should not use the NTP studies as a basis for the dose-response assessment because the test material contained 1% epichlorohydrin, a recognized mutagen and carcinogen. OEHHA considered this issue and concluded that the presence of epichlorohydrin at 1% in the NTP test material could not have substantially affected the 1,3-dichoropropene cancer potency estimate (see p. 14 for a more detailed discussion of this issue). Thus, OEHHA determined the NTP female mouse study meets the criterion in Section 25703 as being a sensitive study of sufficient quality. DPR reached a similar conclusion regarding the test material used in the NTP studies, stating "Epichlorhydrin, which has oncogenic properties of its own, acted as a stabilizer in the 1,3-D *[1,3-dichloropropene]* preparation used in the NTP study.

[94] NTP (1985), full citation provided in footnote 5.
[95] Stott et al. (1987), full citation provided in footnote 6.

However, it is unlikely that it was present in sufficient quantities to be responsible for the observations summarized here"[96].

Alternative 2: An NSRL is not needed because 1,3-dichloropropene is only tumorigenic at levels higher than what humans would be exposed to

Several commenters stated that 1,3-dichloropropene is only tumorigenic at levels higher than what humans would be exposed to. However, it is common for doses used in animal cancer bioassays to be higher than anticipated human exposure levels, sometimes markedly so. The purpose of including high doses in animal studies is not to model expected human exposures, but to ensure adequate power of the study to detect a carcinogenic effect definitively. The BMD method can then be employed to characterize the dose-response relationship by fitting the multistage cancer model to the bioassay data, allowing for estimation of risk in the low dose region.

Commenters also stated that other human health risk analyses have concluded that the current agricultural uses of 1,3-dichloropropene are associated with a reasonable certainty of no harm. It seems the commenters are referring to the process of risk characterization. The purpose of this document is to conduct a dose response assessment, a separate step in risk assessment. The purpose of establishing an NSRL is to provide a level below which the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. If, in the process of risk characterization, it can be soundly demonstrated that agricultural workers or bystanders are exposed to levels below the NSRL, no warnings are required.

Alternative 3: 1,3-Dichloropropene should be treated as a portal-of-entry carcinogen

Dow commented that DPR concluded that 1,3-dichloropropene is a portal-of-entry carcinogen and suggested OEHHA follow DPR's approach. 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"[97]. Both portal-of-entry and systemic exposures may result in lung tumors in mice but a systemic exposure scenario is more likely for the lacrimal gland tumors seen in male mice exposed via inhalation. Therefore, the default

[96] DPR (2015), full citation provided in footnote 11.
[97] *Ibid*.

approach specified in Section 25703(a)(6) was used to adjust for interspecies differences.

Alternative 4: A threshold approach should be used in the cancer dose-response assessment of 1,3-dichloropropene

Commenters stated that the US EPA's Cancer Assessment Review Committee reevaluated the carcinogenic potential of 1,3-dichloropropene based on the new and existing data and downgraded its classification to "Suggestive Evidence of Carcinogenic Potential". They suggested that OEHHA follow US EPA's approach that concluded that "*quantification of human cancer risk is not required*" and recommended that a threshold-based approach will adequately account for all chronic toxicity, including carcinogenicity, that could result from long-term exposure to 1,3-dichloropropene. First, OEHHA does not agree with the US EPA's draft reevaluation of the carcinogenic potential of 1,3-dichloropropene In the letter submitted to the US EPA[98], CalEPA stated that "US EPA's decision to downgrade its prior cancer classification of 1,3-D *[1,3-dichloropropene]* from 'likely to be carcinogenic to humans' to 'suggestive evidence of carcinogenic potential' runs counter to the determination of various regulatory agencies and is unsupported by the agency's exclusive reliance on the 2019 Cancer Assessment Review Committee (CARC) findings… A consequence of this downgrade is that US EPA's cancer guidelines allow a decision not to estimate plausible cancer risks, leaving the public insufficiently informed about the carcinogenicity of 1,3-D and laying the groundwork for less health-protective regulatory controls."

Second, OEHHA does not agree that a threshold approach is appropriate for the dose-response assessment of 1,3-dichloropropene. As described in this ISOR above, consideration of the available mechanistic information on 1,3-dichloropropene, including evidence of genotoxicity, support 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.

[98] CalEPA (2020). Letter to Andrew Wheeler, US EPA. 1,3-Dichloropropene (telone): Draft human health risk assessment for registration review docket no. EPA-HQ-OPP-2013-0154-0102. Available from https://www.regulations.gov/docket/EPA-HQ-OPP-2013-0154/document

Dow stated that blood concentrations of 1,3-dichloropropene in male mice were proportional to inhalation exposure up to levels of 30[99] or 40 ppm[100], above which blood concentrations became nonlinear. This level was deemed the "kinetically-derived maximum tolerated dose" or KMD for short. Dow states that, above the KMD, "probable saturation of GSH [glutathione]-based metabolic clearance" leads to depletion of GSH, which results in decreased metabolic clearance of the test material and a "concomitant increase in the 1,3-D [1,3-dichloropropene] isomers in circulating blood". Dow asserts that, since lung tumors in Lomax et al. (1989)[101,102] were observed only in male mice treated with the highest concentration of 60 ppm, which is above the "threshold" (i.e., the "KMD"), the observed lung tumors are not relevant for human health risk assessment. However, this ignores the fact that lacrimal gland tumors were statistically significantly increased in this male mouse study in the mid-dose group administered 20 ppm, below the "KMD".

Dow stated that chemicals that act via a threshold mechanism require chronic administration and their immediate effects display reversibility and are threshold events. Dow points to a dietary study in male F344 rats in which no tumors were observed at the one-year interim sacrifice, and "late-developing foci" and benign liver tumors only were induced following two-year exposure[103] as providing support for the existence of a threshold. However, a hepatocellular carcinoma was observed in this study in the high-dose group (25.4 mg/kg-day) after 2 years (i.e., study termination), as reported in Stebbins et al. (2000)[104]. Thus, this study does not provide evidence that adenomas cannot progress to carcinomas, and in fact suggests progression from benign to malignant tumors did occur. In a separate study also in male F344 rats[105], increases in the incidence of forestomach squamous cell papilloma or carcinoma (combined) were observed in the dose group receiving 19.1 mg/kg-day, indicating that 1,3-dichloropropene can cause malignant tumors in male rats[106], and at a dose below that

[99] 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.
[100] US EPA (2019). 1,3-Dichloropropene: Report of the Cancer Assessment Review Committee. U.S. Environmental Protection Agency, Washington, DC. PC Code 029001.
[101] Dow referred to this study as Lomax et al. (1987), which reports studies in rats. This is assumed to be a mistake and to actually refer to Stott et al. (1987), which is reported in Lomax et al. (1989).
[102] Lomax et al. (1989), full citation provided in footnote 8.
[103] Stott et al. (1995), full citation provided in footnote 27.
[104] A publication that reported on the studies conducted by Stott et al. 1995. Full citation provided in footnote 24.
[105] NTP (1985), full citation provided in footnote 5.
[106] *Ibid*.

which Dow calls the "KMD". Therefore, Dow's reasoning for a threshold mechanism does not apply.

Several commented that a threshold approach should be used instead of a linear, no-threshold approach to quantitative cancer risk assessment because the overall genotoxicity database for 1,3-dichloropropene is negative. However, as described in this ISOR, genotoxicity of 1,3-dichloropropene has been observed in a number of assays *in vivo* and *in vitro.* The fact that there are negative assays does not negate the findings from positive studies.

Dow stated that positive genotoxicity studies were confounded by the presence of impurities, including epichlorohydrin. However, the mutagenicity of 1,3-dichloropropene has been demonstrated in a number of studies in *Salmonella* conducted with test material free of epichlorohydrin (i.e., individual 1,3-dichloropropene isomers or purified test material), as described above (p. 14). As described above in this ISOR, several metabolites of 1,3-dichloropropene are also genotoxic, including 3-chloro-2-hydroxypropanal and 3-chloroacrolein[107]. Further, a number of genotoxicity studies that tested epichlorohydrin-containing 1,3-dichloropropene formulations were negative, thus it remains uncertain if epichlorohydrin at 1% contributed much, if at all, to the positive genotoxicity findings observed in other studies with epichlorohydrin-containing 1,3-dichloropropene formulations.

Dow also commented that the *in vitro* genotoxicity studies that reported positive results are not considered relevant to *in vivo* situations because the addition of GSH reduces the genotoxic response observed in the *in vitro* assays. However, positive results were reported in *in vivo* studies, including the induction of chromosomal aberrations in bone marrow and micronucleated polychromatic erythrocytes in mice[108].

Dow stated that 1,3-dichloropropane was tested in *in vivo* assays in the Big Blue mouse and rat models and was not mutagenic in the target organs of interest (lung and liver in mice; liver and kidney in rats). However, these studies do not establish the lack of *in vivo* genotoxicity, but only that there is a lack of genotoxicity within the constraints of the assays. There are also a number of limitations; for example, there was no concurrent

[107] DPR (2015), full citation provided in footnote 11.
[108] *Ibid*.

positive control, the *cII* gene has a high spontaneous mutation rate in the liver[109,110], and the assays cited by Dow only examined effects in the lung and liver and did not analyze other target organs such as the forestomach and bladder. Additionally, transgenic animal gene mutations assays are not capable of detecting larger deletions and chromosomal aberrations, which is likely how 1,3-dichloropropene acts. Thus, the Big Blue models do not provide evidence that 1,3-dichloropropene is not genotoxic.

Dow also states that "1,3-D *[1,3-dichloropropene]* exhibits a non-genotoxic mode of tumorigenic action in the rat liver and mouse lung by promoting the development of adenomas from spontaneously initiated cells within these tissues (Klaunig *et al*., 2015)", suggesting that 1,3-dichloropropene acts as a promoter. Klaunig et al. (2015)[111] was a promotion study in which F344 rats were pretreated with diethylnitrosamine to induce preneoplastic lesions in the liver then administered 25 mg/kg-day 1,3-dichloropropene via gavage for 30 days, 60 days, or 30 days followed by a 30-day recovery period. Treatment with 1,3-dichloropropene increased the number and size of glutathione S-transferase (GSTP)-negative foci in the liver, which returned to control levels after a 30-day recovery period. The authors concluded that 1,3-dichloropropene induces "liver carcinogenesis through a nongenotoxic mode of action by functioning as a tumor promoter specifically through induction of a non-GSTP staining focal hepatocyte population"[112]. However, this study does not provide conclusive evidence that 1,3-dichloropropene acts only as a promoter or strictly through a non-genotoxic mechanism in the mouse lung and rat liver for several reasons. First, since the total duration was ≤ 60 days, there was insufficient time to develop any tumors. Thus, they could not demonstrate that the liver foci progressed to tumors or that tumors arose from other areas of the liver or in other organs. Second, this study was conducted male rats and tissue examination was limited to the liver, thus this study provides no information on the mechanism of tumor induction by 1,3-dichloropropene in other organs in the male rat, or in female rats, or in other species. As shown in Table 1 above, 1,3-dichloropropene induces not only liver tumors, but also forestomach and adrenal gland tumors in male rats; liver and mammary gland tumors in female rats; lung,

[109] Nohmi T, Masumura K, Toyoda-Hokaiwado N (2017). Transgenic rat models for mutagenesis and carcinogenesis. *Genes and environment: the official journal of the Japanese Environmental Mutagen Society 39:*11.
[110] Chen T, Gamboa da Costa G, Marques MM, Shelton SD, Beland FA, Manjanatha MG (2002). Mutations induced by alpha-hydroxytamoxifen in the lacI and cII genes of Big Blue transgenic rats. *Carcinogenesis* 23:1751-7.
[111] Klaunig JE, Gehen SC, Wang Z, Klein PJ, Billington R (2015). Mechanism of 1,3 Dichloropropene-Induced Rat Liver Carcinogenesis. *Toxicol Sci*. 143(1): 6–15.
[112] *Ibid*.

lacrimal gland and liver tumors in male mice; and urinary bladder, lung, and forestomach tumors in female mice. As described above, 1,3-dichloropropene was positive in a number of genotoxicity assays; moreover, carcinogens often act through more than one mechanism[113]. For these reasons, the Klaunig et al. (2015) study cited by Dow does not show that 1,3-dichloropropene acts only as a promoter or through a non-genotoxic mechanism.

Alternative 5: Multiple dichotomous models in US EPA's BMDS software should be run and the model with the lowest Akaike information criterion (AIC) should be chosen

Dow proposed modeling the cancer dose-response data with eight different dichotomous models available in US EPA's BMDS software, and using the results from the model with the lowest AIC to derive the NSRL. OEHHA does not agree with this approach because it is not appropriate to use just any model for cancer dose-response analysis. The multistage model is generally accepted as the default approach to modeling lifetime cancer bioassay data, unless there is strong evidence supporting an alternative model. Use of the multistage model for cancer dose-response analyses is consistent with Section 25703, with scientific practice in other OEHHA programs[114], with other scientific guidance, including US EPA's 2005 cancer risk assessment guidelines[115], and with US EPA's scientific practice[116,117].

Alternative 6: The NSRL should be based on oral gavage data because inhalation studies were not the basis for listing

Dow asserted that an NSRL for 1,3-dichloropropene must be based on oral data because the chemical was listed by the State's Qualified Experts on the basis of gavage data, and not on the basis of inhalation studies. OEHHA does not agree with Dow's assertion that an NSRL for 1,3-dichloropropene should not be developed based on data

[113] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 124:713-721.
[114] 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
[115] US EPA (2005), full citation provided in footnote 63.
[116] US EPA (2012). US Environmental Protection Agency. Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4). Integrated Risk Information System (IRIS). Washington, DC. EPA/635/R-08/011F. February 2011.
[117] US EPA (2011). US Environmental Protection Agency. Toxicological Review of Trichloroacetic Acid (CAS No. 76-03-9). Integrated Risk Information System (IRIS). Washington, DC. EPA/635/R-09/003F. September 2011.

from inhalation studies. The listing of 1,3-dichloropropene under Proposition 65 is not limited with respect to the route of exposure. Moreover, as summarized in Table 1, 1,3-dichloropropene induces tumors in animals when administered by the inhalation route, as well as by the oral route. Therefore, OEHHA is proposing the adoption of NSRLs for the oral and inhalation routes for 1,3-dichloropropene.

In conclusion, for the reasons stated here, OEHHA has determined that there is no alternative to the proposed regulation that is less burdensome and equally effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed NSRLs by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)) so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed NSRLs provide “safe harbor” levels for businesses to use when determining compliance with Proposition 65, OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulatory action given that use of the NSRLs is entirely voluntary and the NSRLs only provide compliance assistance for businesses subject to the Act.

Impact on the Creation or Elimination of Jobs/Businesses in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. 1,3-Dichloropropene is listed under Proposition 65; therefore, businesses that manufacture, distribute, sell or use products with 1,3-dichloropropene in the state must provide a warning if their product or activity exposes the public or employees to significant amounts of the chemical. The regulatory proposal does not create additional compliance requirements, but instead provides "safe harbor" values that aid businesses in determining whether a warning is required for a given exposure.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California: This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides "safe harbor" values that aid businesses in determining if they are complying with the law.

Impact on Expansion of Businesses within the State of California: This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides "safe harbor" values that aid businesses in determining if they are complying with the law.

Benefits of the Proposed Regulation: The NSRLs provide "safe harbor" values that aid businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing an NSRL and therefore may be subjected to litigation for a failure to warn of an exposure to or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing safe harbor levels, this

regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their products or releases from their facilities to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.

Appendix A

Data extracted from Stott et al. (1987) that were relied on by the Office of Environmental Health Hazard Assessment to calculate a cancer potency and NSRL (inhalation route) for 1,3-dichloropropene.

Table A1. Average body weight from the control group of male mice (Stott et al. 1987)

Days on test	Body weight (g)	Days on test	Body weight (g)
7	24.4	258	31.0
13	25.8	286	31.3
20	26.0	314	31.6
27	26.1	342	32.0
34	26.7	370	31.2
41	27.5	398	31.5
48	27.6	426	31.2
55	28.3	454	32.0
62	28.5	482	32.0
69	28.5	510	32.9
76	28.9	538	33.4
83	29.3	566	33.1
90	28.9	594	34.0
118	29.6	622	33.0
153	31.0	650	32.8
174	31.6	678	30.9
202	32.0	706	31.1
230	32.1	734	30.7

Table A2. Tumors observed in the lungs (bronchioloalveolar adenoma or adenocarcinoma) and lacrimal gland (cystadenoma or carcinoma) in the male mouse study by Stott et al. (1987)

Animal number	Treatment group[a]	Lungs	Lacrimal gland	Days on study
84A0312	control	bronchioloalveolar adenoma	no tumor	736
84A0313	control	bronchioloalveolar adenoma	no tumor	730
84A0314	control	no tumor	no tumor	736
84A0317	control	no tumor	no tumor	736
84A0318	control	no tumor	no tumor	736
84A0320	control	no tumor	no tumor	736
84A0323	control	bronchioloalveolar adenoma	no tumor	736
84A0326	control	no tumor	no tumor	736
84A0327	control	no tumor	no tumor	736
84A0329	control	no tumor	no tumor	736
84A0330	control	no tumor	no tumor	736
84A0332	control	no tumor	no tumor	736
84A0333	control	no tumor	no tumor	736
84A0334	control	no tumor	no tumor	736
84A0335	control	no tumor	no tumor	736
84A0336	control	no tumor	no tumor	736
84A0337	control	no tumor	no tumor	736
84A0338	control	no tumor	no tumor	736
84A0339	control	bronchioloalveolar adenoma	no tumor	736
84A0341	control	no tumor	no tumor	736
84A0342	control	no tumor	no tumor	736
84A0343	control	no tumor	no tumor	738
84A0345	control	no tumor	no tumor	738
84A0346	control	bronchioloalveolar adenoma	no tumor	738
84A0348	control	no tumor	no tumor	738
84A0350	control	no tumor	no tumor	738
84A0352	control	bronchioloalveolar adenoma	no tumor	738
84A0353	control	bronchioloalveolar adenoma	no tumor	738
84A0354	control	no tumor	no tumor	738
84A0355	control	no tumor	cystadenoma	738
84A0356	control	no tumor	no tumor	738
84A0357	control	no tumor	no tumor	738
84A0358	control	no tumor	no tumor	738
84A0359	control	no tumor	no tumor	738

Animal number	Treatment group[a]	Lungs	Lacrimal gland	Days on study
84A0360	control	no tumor	no tumor	738
84A0361	control	no tumor	no tumor	738
84A0363	control	no tumor	no tumor	694
84A0365	control	no tumor	no tumor	738
84A0366	control	no tumor	no tumor	738
84A0367	control	no tumor	no tumor	670
84A0368	control	no tumor	no tumor	739
84A0370	control	no tumor	no tumor	739
84A0371	control	bronchioloalveolar adenoma	no tumor	739
84A0372	control	no tumor	no tumor	25
84A0373	control	no tumor	no tumor	739
84A0374	control	no tumor	no tumor	739
84A0376	control	no tumor	no tumor	739
84A0377	control	bronchioloalveolar adenoma	no tumor	739
84A0378	control	no tumor	no tumor	739
84A0379	control	no tumor	no tumor	739
84A0380	20.9	no tumor	carcinoma	736
84A0381	20.9	no tumor	no tumor	736
84A0382	20.9	no tumor	no tumor	736
84A0383	20.9	no tumor	no tumor	736
84A0384	20.9	no tumor	no tumor	736
84A0385	20.9	no tumor	cystadenoma	736
84A0386	20.9	no tumor	no tumor	690
84A0387	20.9	bronchioloalveolar adenoma	no tumor	736
84A0388	20.9	no tumor	no tumor	547
84A0391	20.9	no tumor	no tumor	736
84A0392	20.9	no tumor	no tumor	736
84A0393	20.9	no tumor	no tumor	736
84A0395	20.9	bronchioloalveolar adenoma	no tumor	736
84A0396	20.9	no tumor	no tumor	736
84A0397	20.9	no tumor	no tumor	736
84A0398	20.9	no tumor	cystadenoma	736
84A0400	20.9	no tumor	no tumor	736
84A0403	20.9	no tumor	no tumor	736
84A0404	20.9	bronchioloalveolar adenoma	no tumor	736
84A0406	20.9	no tumor	no tumor	736
84A0410	20.9	no tumor	cystadenoma	736

Animal number	Treatment group[a]	Lungs	Lacrimal gland	Days on study
84A0412	20.9	no tumor	no tumor	736
84A0413	20.9	no tumor	no tumor	736
84A0414	20.9	no tumor	no tumor	738
84A0416	20.9	bronchioloalveolar adenoma	no tumor	738
84A0417	20.9	no tumor	no tumor	738
84A0419	20.9	no tumor	no tumor	738
84A0420	20.9	no tumor	no tumor	738
84A0421	20.9	no tumor	no tumor	738
84A0422	20.9	no tumor	no tumor	738
84A0424	20.9	no tumor	no tumor	738
84A0427	20.9	no tumor	no tumor	738
84A0428	20.9	no tumor	no tumor	738
84A0429	20.9	no tumor	no tumor	738
84A0431	20.9	no tumor	no tumor	738
84A0432	20.9	no tumor	cystadenoma	738
84A0433	20.9	no tumor	cystadenoma	738
84A0434	20.9	no tumor	no tumor	670
84A0435	20.9	bronchioloalveolar adenoma	no tumor	738
84A0436	20.9	no tumor	no tumor	738
84A0438	20.9	no tumor	no tumor	739
84A0439	20.9	no tumor	cystadenoma	626
84A0440	20.9	no tumor	no tumor	739
84A0441	20.9	no tumor	no tumor	739
84A0442	20.9	no tumor	no tumor	694
84A0443	20.9	no tumor	no tumor	739
84A0444	20.9	bronchioloalveolar adenoma	no tumor	739
84A0445	20.9	no tumor	no tumor	739
84A0446	20.9	no tumor	no tumor	739
84A0447	20.9	no tumor	no tumor	739
84A0450	83.6	no tumor	no tumor	736
84A0451	83.6	no tumor	cystadenoma	736
84A0453	83.6	bronchioloalveolar adenoma	no tumor	681
84A0454	83.6	no tumor	no tumor	736
84A0455	83.6	bronchioloalveolar adenoma	cystadenoma	736
84A0458	83.6	no tumor	no tumor	694
84A0459	83.6	no tumor	cystadenoma	736
84A0460	83.6	no tumor	no tumor	736

Animal number	Treatment group[a]	Lungs	Lacrimal gland	Days on study
84A0461	83.6	no tumor	no tumor	680
84A0463	83.6	no tumor	cystadenoma	736
84A0464	83.6	no tumor	no tumor	736
84A0465	83.6	no tumor	no tumor	736
84A0467	83.6	bronchioloalveolar adenoma	cystadenoma	736
84A0468	83.6	no tumor	no tumor	736
84A0469	83.6	no tumor	no tumor	736
84A0472	83.6	no tumor	no tumor	687
84A0473	83.6	bronchioloalveolar adenoma	cystadenoma	736
84A0474	83.6	bronchioloalveolar adenoma	no tumor	736
84A0475	83.6	no tumor	cystadenoma	736
84A0476	83.6	no tumor	no tumor	736
84A0477	83.6	bronchioloalveolar adenoma and adenocarcinoma	no tumor	736
84A0478	83.6	no tumor	no tumor	736
84A0480	83.6	no tumor	no tumor	736
84A0481	83.6	bronchioloalveolar adenoma	no tumor	736
84A0482	83.6	no tumor	no tumor	738
84A0483	83.6	no tumor	cystadenoma	738
84A0485	83.6	no tumor	no tumor	738
84A0486	83.6	no tumor	no tumor	738
84A0487	83.6	bronchioloalveolar adenoma	no tumor	738
84A0488	83.6	no tumor	no tumor	738
84A0490	83.6	no tumor	no tumor	738
84A0491	83.6	no tumor	no tumor	738
84A0493	83.6	bronchioloalveolar adenoma	no tumor	738
84A0494	83.6	no tumor	cystadenoma	738
84A0495	83.6	bronchioloalveolar adenoma	no tumor	738
84A0498	83.6	no tumor	no tumor	738
84A0500	83.6	no tumor	no tumor	738
84A0502	83.6	no tumor	no tumor	738
84A0503	83.6	no tumor	no tumor	346
84A0504	83.6	no tumor	no tumor	738
84A0505	83.6	bronchioloalveolar adenoma	no tumor	738
84A0509	83.6	no tumor	no tumor	738
84A0510	83.6	no tumor	no tumor	739
84A0511	83.6	bronchioloalveolar adenoma	no tumor	739

Animal number	Treatment group[a]	Lungs	Lacrimal gland	Days on study
84A0512	83.6	no tumor	no tumor	739
84A0513	83.6	no tumor	cystadenoma	739
84A0514	83.6	no tumor	no tumor	739
84A0516	83.6	no tumor	no tumor	739
84A0518	83.6	bronchioloalveolar adenoma	no tumor	739
84A0519	83.6	no tumor	no tumor	739
84A0520	251	no tumor	no tumor	736
84A0521	251	bronchioloalveolar adenoma	no tumor	736
84A0524	251	bronchioloalveolar adenoma	no tumor	736
84A0526	251	bronchioloalveolar adenoma	no tumor	736
84A0527	251	bronchioloalveolar adenoma	no tumor	736
84A0528	251	no tumor	no tumor	736
84A0529	251	no tumor	no tumor	736
84A0530	251	no tumor	no tumor	736
84A0531	251	no tumor	carcinoma	736
84A0534	251	no tumor	no tumor	736
84A0535	251	bronchioloalveolar adenoma	no tumor	736
84A0536	251	no tumor	no tumor	736
84A0537	251	bronchioloalveolar adenoma	no tumor	736
84A0538	251	no tumor	no tumor	736
84A0539	251	no tumor	no tumor	736
84A0540	251	bronchioloalveolar adenoma	no tumor	736
84A0543	251	no tumor	no tumor	736
84A0545	251	bronchioloalveolar adenoma	cystadenoma	736
84A0546	251	no tumor	no tumor	736
84A0548	251	no tumor	cystadenoma	736
84A0549	251	no tumor	no tumor	738
84A0550	251	bronchioloalveolar adenoma	no tumor	558
84A0551	251	bronchioloalveolar adenoma	no tumor	738
84A0552	251	bronchioloalveolar adenoma	no tumor	738
84A0553	251	no tumor	no tumor	646
84A0554	251	no tumor	no tumor	738
84A0555	251	bronchioloalveolar adenoma	no tumor	738
84A0556	251	bronchioloalveolar adenoma	no tumor	738
84A0558	251	no tumor	no tumor	738
84A0561	251	no tumor	no tumor	738
84A0562	251	no tumor	no tumor	738

Animal number	Treatment group[a]	Lungs	Lacrimal gland	Days on study
84A0563	251	no tumor	no tumor	738
84A0565	251	no tumor	cystadenoma	738
84A0569	251	no tumor	no tumor	738
84A0571	251	no tumor	no tumor	738
84A0572	251	bronchioloalveolar adenoma	no tumor	738
84A0573	251	bronchioloalveolar adenoma	no tumor	738
84A0574	251	no tumor	no tumor	738
84A0575	251	bronchioloalveolar adenoma	no tumor	738
84A0577	251	no tumor	no tumor	739
84A0578	251	no tumor	cystadenoma	739
84A0579	251	bronchioloalveolar adenoma	no tumor	739
84A0580	251	no tumor	no tumor	739
84A0582	251	bronchioloalveolar adenoma	cystadenoma	590
84A0583	251	no tumor	no tumor	739
84A0584	251	bronchioloalveolar adenoma	no tumor	739
84A0585	251	bronchioloalveolar adenoma	no tumor	739
84A0586	251	bronchioloalveolar adenoma	no tumor	739
84A0588	251	bronchioloalveolar adenoma	no tumor	739
84A0589	251	no tumor	no tumor	739

[a] Treatment groups: control, low-, mid-, and high- dose, expressed as mg/m^3 1,3-dichloropropene

Appendix B

Information extracted from Kelly (1997)[118] and Kelly (1998)[119] that were used by the Office of Environmental Health Hazard Assessment in determining the most sensitive studies of sufficient quality for calculating a cancer potency and NSRL for 1,3-dichloropropene.

Kelly (1997)

Male and female CD-1 mice (65/sex/group) were administered 0, 2, 10, or 25 mg/kg-day 1,3-dichloropropene (reported as DD-92) via gavage for up to 18 months. Doses were administered once daily, 7 days per week. The test substance, in liquid form, was supplied by the American Cyanamid Company and reported to be 94.8% purity, with dosages "adjusted to correct for purity". Control animals received the vehicle (corn oil) at the same dose volume as administered to treated groups. No tumors were reported in male mice. In female mice, there was a slight increase in benign submucosal mesenchymal tumors in the urinary bladder in the high dose group that was not statistically significantly increased compared to controls.

Kelly (1998)

Male and female Sprague-Dawley CD rats (75/sex/group) were administered 0, 2, 10, or 25 mg/kg-day 1,3-dichloropropene (reported as DD-92) via gavage for up to 24 months. Male and female rats were sacrificed at 23 and 24 months, respectively. Doses were administered once daily, 7 days per week. The test substance, in liquid form, was supplied by the American Cyanamid Company and reported to be 94.8% purity, with dosages "adjusted to correct for purity". Control animals received the vehicle (corn oil) at the same dose volume as administered to treated groups. No tumors were reported for male or female rats.

[118] Kelly CM (1997), full citation provided in footnote 23.
[119] Kelly CM (1998), full citation provided in footnote 26.