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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: 1,3-Dichloropropene **CAS REGISTRY NUMBER:** 542-75-6

AMBIENT WATER QUALITY VALUE: 0.4 ug/L *

* Applies to the sum of cis- and trans-1,3-dichloropropene, CAS Nos. 10061-01-5 and 10061-02-6, respectively.

BASIS: Oncogenic

SUMMARY OF INFORMATION

1,3-Dichloropropene (1,3-DCP) is the active ingredient in Telone, Telone II, and D-D, registered trademarks of Dow Chemical Company. They are used as broad spectrum soil fumigants to control nematodes. Telone is 40% cis- and 38% trans- isomers. Telone II is 48-53% cis- and 42-45% trans-isomers. D-D is 25-28% cis-, 25-27% trans-, and 25-29% 1,2-dichloropropane (ATSDR, 1992). Most of the toxicological data on 1,3-dichloropropene are from studies of exposure to formulations.

Pharmacokinetics

1,3-Dichloropropene is readily absorbed, metabolized and excreted in humans. Men exposed to 1,3-DCP during soil fumigation were monitored for the urinary metabolites of cis- and trans-1,3-dichloropropene, N-acetyl-S-(cis- and trans-3-chlorophenyl-2)-1-cysteine. Half lives of elimination were short, 5 hours for both the cis- and trans- forms. cis-1,3-DCP yielded three times more of its metabolites than did trans-1,3-DCP, probably due to differences in rates of metabolism (Van Welie et al., 1991).

Rats injected with cis- or trans-1,3-DCP isomers excreted 55% and 45% of the doses as

the respective N-acetyl-(cis- or trans-3-chlorophenyl-2-)-L-cysteine metabolites. The trans-isomer is metabolized at a slower rate than the cis- to mercapturic acid and is converted to a greater extent to CO_2 and exhaled. Upon oral administration of cis- and trans-1,3-DCP to rats, 80% of cis- and 56% of trans-isomers were eliminated in urine. About 4% of cis- and 24% of trans-1,3-DCP-^{14}C doses yielded (^{14}C) CO_2 in the exhaled air (Hutson et al., 1971; Climie et al., 1979).

Exposed rats metabolize 1,3-DCP predominantly by conjugation with glutathione (GSH). The conjugate is detectable in the blood (Fisher and Kilgore, 1989). The glutathione conjugate is further metabolized to the corresponding mercapturic acid, which is excreted (Climie et al., 1979). This conversion acts as a detoxification mechanism. In tissues depleted of GSH, the extent of covalent binding of 1,3-DCP to macromolecules correlated with the decrease in GSH content (Dietz et al., 1984; Fisher and Kilgore, 1989). Since both isomers form the same intermediates it is reasonable to assume they form the same active intermediate in covalent binding. The isomers may thus be regulated as one compound, 1,3-dichloropropene.

Acute Toxicity

An LD_{50} value of 150 mg/kg was reported for Telone II in Sprague-Dawley rats. The LD_{50} for the cis-isomer of 1,3-dichloropropene for male and female rats combined was 121 mg/kg; for males only, 126 mg/kg; for females only, 117 mg/kg (Jones and Collier, 1986; Jones 1988, both as cited in ATSDR, 1992).

Following acute inhalation exposure, the major organs to show acute tissue injury are the kidneys, liver and lungs (Torkelson and Rowe, 1981). After exposure of Fischer 344 rats to 0, 25, 50 or 75 mg/kg 1,3-dichloropropene intraperitoneally, renal injury was suggested by the release of N-acetyl glucosaminidase, significantly increased at the higher levels of 1,3-DCP (Osterloh and Xiwen, 1990).

Chronic Toxicity

In Dutch workers applying 1,3-DCP in flower bulb culture, total serum bilirubin was significantly decreased from 9.5 at the start to 7.0 umol/L after the end of the growing season and serum gamma glutamyltranspeptidese increased, indicating moderate hepatic enzyme induction. A subclinical nephrotoxic response was indicated by an increase in serum albumin, decrease in creatinine excretion and increase in retinol binding protein. Glutathione conjugation was impaired as indicated by decreases in glutathione-S-transferase in erythrocytes and glutathione in blood (Brouwer et al., 1991).

Effects induced in animals after subchronic inhalation exposure to 1,3-DCP include damage to the nasal epithelium, hyperplasia of the respiratory epithelium, hyperplasia of the urinary bladder and change of organ weights relative to controls. (Stott et al., 1988; Lomax et al., 1989). In rats exposed by gavage to Telone at 0, 1, 3, 10 or 30 mg/kg/day for 90 days, the relative weight of the kidney of males was higher than controls at the 10 and 30 mg/kg/day exposures (Til et al., 1973).

Male and female Fischer 344 rats and $B6C3F_1$ mice were exposed by inhalation to target concentrations of 0, 5, 20 or 60 ppm (0, 22.7, 90.8 or 272 mg/m^3) of technical 1,3-dichloropropene 6 hr/d, 5 d/wk, up to 2 years (Lomax, et al., 1989). Significant nonneoplastic changes were morphological alterations in the nasal tissues of rats exposed to 60 ppm and mice exposed to 20 or 60 ppm 1,3-DCP. Mice exposed to 20 or 60 ppm had hyperplasia of the transitional epithelium lining the urinary bladder. Also observed was an increased incidence of benign lung tumors (bronchioalveolar adenomas) in male mice exposed to 60 ppm 1,3-DCP.

USEPA (1988a; 1994a) derived an RfD (equivalent to an acceptable daily intake) on the basis of increased organ weights in rats exposed orally to 0, 1, 3, 10, or 30 mg/kg/day 1,3-DCP for 90 days. Increased kidney weights were noted in 10 and 30 mg/kg/day males (Til et al., 1973). USEPA chose a NOAEL of 3 mg/kg/day. An RfD of 0.3 ug/kg was calculated using procedures equivalent to 6 NYCRR 702.5(b) which would yield a water quality value of 2.1 ug/L.

Reproductive Toxicity

In a two-generation inhalation study of Fischer 344 rats exposed to 0, 52, 154 or 464 mg/m^3 1,3-DCP technical 6 hr/d, 5 d/wk, exposure did not adversely affect the reproductive and neonatal parameters evaluated (Breslin et al., 1989).

Linnett et al., (1988) assessed reproductive effects on rats after 10 weeks exposure to 0, 52, 154 or 464 mg/m^3 inhaled D-D (1,3-DCP/1,2-DCP) 6 hr/d, 5 d/wk and found no adverse effects on libido, fertility or morphology of the reproductive tracts of either sex and no dominant lethal effects in males.

In rats exposed to 0, 91, 272 or 545 mg/m^3 1,3-DCP for 6 h/day on days 6-15 of gestation, no dose-related effects on reproductive performance were noted. There was no evidence of teratogenic or embryotoxic response at any dose (WHO, 1993).

Genotoxicity

1,3-Dichloropropene possesses direct alkylating properties and exerts direct mutagenicity. It forms DNA adducts in vitro, in isolated perfused liver and in vivo in mice (Eder, 1991; 1987). A dose-dependent frequency of DNA single strand breaks was seen in V79 Chinese hamster cells and in liver, kidney, and gastric mucosa of rats (Ghia et al., 1993; Brambilla et al., 1992). In primary cultures of rat and human hepatocytes, similar amounts of DNA

fragmentation and DNA repair were seen. After glutathione depletion, an increase of DNA breaks was observed (Martelli et al., 1992, 1993).

The cis- and trans-isomers of 1,3-DCP have been found active in S. typhimurium strains TA1535, 1537, 1538, 100, 98 and 1978 with or without activation by several authors (Creedy et al. 1984, De Lorenzo et al., 1977, Eder et al., 1982, Haworth et al., 1983, Neudecker et al., 1977, 1980; Stolzenburg and Hine, 1980, Vithayathil et al., 1983 all as cited in ATSDR, 1992). Sister chromatid exchange was found in Chinese hamster ovary cells with technical 1,3-DCP (Loveday et al., 1989) and in V79 cells with both isomers (von de Hude et al., 1987).

Carcinogenicity

No studies and no data on human carcinogenicity were found.

NTP (1985) exposed male and female rats and mice to Telone II containing 89% cis- and trans-1,3-dichloropropene, 2.5% 1,2-dichloropropane, 1.5% of trichloropropene isomers and 1.0% epichlorohydrin. In male F344/N rats exposed to 0, 25 or 50 mg/kg Telone II by gavage 3 times a week, NTP (1985) found clear evidence of carcinogenicity, as indicated by compound related increased incidences of squamous cell papilloma and carcinoma of the forestomach and increased incidence of neoplastic nodules of the liver. In female F344/N rats, there was some evidence of carcinogenicity as Telone II caused an increased incidence of squamous cell papillomas of the forestomach. There was clear evidence of carcinogenicity for female $B6C3F_1$ mice because Telone II caused increased incidences of transitional cell carcinomas of the urinary bladder, alveolar/bronchiolar adenomas of the lung and squamous cell papillomas or carcinomas of the forestomach (Table I). The study on male mice was considered inadequate because of reduced survival in the vehicle control group.

USEPA (1988a) assessed cancer risk due to 1,3-DCP on the basis of increased incidence of squamous cell papillomas and carcinomas of the forestomach in male rats exposed to 1,3-DCP for 2 years (NTP, 1985). Using data from this study and the linearized multistage model, equivalent to procedures in 6 NYCRR 702.4, a carcinogenic potency factor (q^*_1) for humans of 1.75×10^{-1} $(mg/kg/day)^{-1}$ was calculated for an increased cancer risk of one in one million (USEPA, 1988a). U.S. EPA has withdrawn this value because the calculation cannot be reproduced.

The basis of the value has been revised, using data from NTP (1985). Data sets from male rats (liver, stomach) and female mice (stomach, lung, bladder) were pooled to give a combined tumor data set. Using this data and the linearized multi-stage model a new carcinogenic potency factor for humans of 1.8×10^{-1} $(mg/kg/day)^{-1}$ was calculated (USEPA 1994b).

TABLE I. Tumor Incidence in Telone II-exposed Rats and Mice (NTP, 1985)

Animal	TWA Dose (mg/kg/d)[1]	Tumor Type	Tumor Incidence
male rats	0 10.7 21.4	papillomas or carcinomas of forestomach	1/52 1/52 13/52
male rats	0 10.7 21.4	neoplastic nodules of liver	1/52 6/52 8/52
female rats	0 10.7 21.4	papillomas forestomach	0/52 2/52 3/52
female mice	0 21.4 42.8	squamous cell papillomas or carcinoma forestomach	0/50 1/50 4/47
female mice	0 21.4 42.8	transitional cell carcinomas of urinary bladder	0/50 8/50 21/48
female mice	0 21.4 42.8	alveolar/bronchiolar adenomas or carcinomas	2/50 4/50 8/50
male mice	0 21.4 42.8	alveolar/bronchiolar adenomas or carcinomas	1/50 13/50 12/50

[1] Doses transformed to mg/kg/day.

DERIVATION OF VALUES

The NTP (1985) finding of clear evidence of carcinogenicity after exposure to 1,3-DCP (Telone II) in male rats and female mice at multiple sites in a well-conducted bioassay with adequate dosing fulfills the definition of an oncogenic effect in 700.1 for 1,3-dichloropropene. Therefore, a water quality value can be derived for 1,3-DCP using section 702.4 procedures based on oncogenic effects.

1. Selection of Data

Based on tumor type, route, duration of exposure and statistical significance of tumor incidences the NTP, 1985 bioassay is selected as the most appropriate dose-response data for deriving a value. A summary of the data sets showing statistically and biologically significant increases in tumor response is presented in Table I.

2. Selection of Model

For the derivation of a water quality value for an identified carcinogen, Part 702 specifies use of the linear multi-stage (LMS) low-dose extrapolation model unless there is sufficient evidence that supports use of another extrapolation procedure. The GLOBAL82 LMS model (Howe and Crump, 1982) is chosen to estimate the doses corresponding to the 10^{-6} lifetime excess cancer risk of exposure to 1,3-DCP in animals. Both the 95 percent lower confidence limit (LCL) and maximum likelihood estimate (MLE) are calculated for the animal dose associated with the $1x10^{-6}$ lifetime excess cancer risk (Table II). The MLE, when compared to the LCL, provides a measure of goodness-of-fit of the data.

3. Conversions

The output of the GLOBAL82 extrapolation, which is the animal dose associated with a $1x10^{-6}$ excess cancer risk, is converted to a human dose by surface area (S.A.) conversion as specified in Part 702. Pharmacokinetic data are lacking and there appears to be no compelling reason for using an alternative conversion procedure.

$$\text{Human dose} = \left(\frac{\text{animal body weight}}{\text{human body weight}} \right)^{0.33} \times \text{animal dose}$$

Human doses for all data sets are shown in Table III. Human daily doses are converted to water quality values that are based on lifetime exposure of a 70 kg human consuming 2 liters of water per day.

Table II. Animal Dose Associated with 10^{-6} Risk

Data Set		Animal Dose ug/kg/day GLOBAL 82	
Animal	Tumor Site	95% LCL	MLE
male rat	forestomach	.140	44
female rat	forestomach	.161	65
male rat	liver	.081	.138
female mice	forestomach	.161	65
female mice	urinary bladder	.072	.41
female mice	lung	.183	1.8
male mice	lung	.087	.12

Table III. Human Dose and Water Quality Value at 10^{-6} Risk

Data Set		Conversion Factor[1]	95% LCL Human Dose (ug/kg/day)	Water Value (ug/L)
Animal	Site			
male rat	forestomach	.18	.0252	0.9
female rat	forestomach	.16	.0258	0.9
male rat	liver	.18	.0146	0.5
female mice	forestomach	.084	.0135	0.5
female mice	urinary bladder	.084	.006	0.2
female mice	lung	.084	.0154	0.5
male mice	lung	.085	.0074	0.3

[1] Conversion Factor = $\left(\frac{\text{animal bw}}{\text{human bw}}\right)^{0.33}$

where
- weight of male rats = 0.40 kg[2]
- weight of female rats = 0.250 kg[2]
- weight of male mouse = 0.040 kg[2]
- weight of female mouse = 0.038 kg[2]
- weight of adult human = 70 kg
- surface area scaling factor = 0.33

[2] USEPA, 1988b

4. Values and Uncertainties

   Results of the quantitative risk assessment based on male and female tumor incidence data from the NTP (1985) bioassay are presented in Tables II and III. Human doses based on the 95% lower confidence limit (LCL) of individual data sets range from 0.006 ug/kg/day to 0.0258 ug/kg/day for the various sites with increases in tumor incidences. The female mouse urinary bladder is the most sensitive site in the most sensitive species according to these outputs from the LMS model. The occurrence of tumors was significant at all doses. Values based on both the lower confidence limit and the maximum likelihood estimate (MLE) are provided, although only the former meet the Part 702 requirements as a basis for a value. The small difference between the MLEs and LCLs for the urinary bladder individual data suggest a lower degree of uncertainty in predicting risk for the 10^{-6} level.

5. Selection of Value

   Based on the female mice urinary bladder data, a risk estimate based water quality value of 0.2 ug/L can be selected as the most stringent that can be derived.

ADJUSTMENT TO DERIVATION OF VALUE

The above value was derived in 1994 using an interspecies scaling of doses based on the 2/3 power of relative body weights, as specified in 6 NYCRR Part 702. As proposed in Part 702, the Department is revising the interspecies scaling to be done on the basis of the 3/4 power of relative body weights. Accordingly, the ambient water quality value is recalculated from the female mouse urinary bladder dose as shown:

$$\text{Human dose} = (0.072 \text{ ug/kg/day}) \left(\frac{0.038}{70}\right)^{0.25} = 0.011 \text{ ug/kg/day}$$

$$\text{Ambient water quality value} = \frac{(0.011 \text{ ug/kg/day})\ (70 \text{ kg})}{2\text{L}} = 0.385 \text{ ug/L, rounded to } 0.4 \text{ ug/L}$$

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SEARCH STRATEGY

RTECS. Searched 9/93.
CCRIS. Searched 9/93.
IRIS. Searched 2/94.
Database searches on Toxline, Biosis and NTIS. 9/93.

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