Fact Sheet Date: March 12, 1998

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: 1,2,3-Trichloropropane **CAS REGISTRY NUMBER:** 96-18-4

AMBIENT WATER QUALITY VALUE: 0.04 ug/L

BASIS: Oncogenic

SUMMARY OF INFORMATION

1,2,3-Trichloropropane ($C_3H_5Cl_3$) (1,2,3-TCP) is used as a paint and varnish remover, solvent and degreasing agent and a cross-linking agent in the synthesis of polysulfides and hexafluoropropylene (USEPA, 1989).

The toxicologic database for this compound has been reviewed (ATSDR, 1992; IRIS, 1994; NTP, 1983, 1993; USEPA, 1989).

Pharmacokinetics

No information on the absorption, metabolism or excretion of 1,2,3-TCP in humans was found.

Following acute oral exposure of male and female rats (30 mg/kg) and male mice (30, 60 mg/kg), ^{14}C-1,2,3-TCP was rapidly adsorbed, metabolized and excreted (Volp et al., 1984). Adipose tissue accumulated the largest part (37%) of the dose within 15 minutes and retained more of the dose than any other tissue until 4 hr. After 4 hr, ^{14}C-TCP disappeared from adipose tissue while metabolites appeared in the liver and other tissues. 1,2,3-TCP-derived radioactivity was most concentrated in the liver, kidney and forestomach in both rats and mice.

By 60 hr, excretion was nearly complete (95%) and was predominately through the urine. Rats excreted 50% and mice 60% of the radioactivity in the urine. Two urinary metabolites were isolated and identified, N-acetyl- and S-(3-chloro-2-hydroxypropyl) cysteine. The major biliary metabolite was 2-(S-glutathionyl) malonic acid. Expiration was the only route by which unchanged 1,2,3-TCP was excreted. In addition, 25% of the dose was expired as CO_2. Excretion in the feces accounted for 20% of the dose in 60 hr rats and 15% in mice (Mahmood et al., 1988, 1991; Volp et al., 1984).

Weber and Sipes (1990) investigated the role of biotransformation in 1,2,3-TCP induced tumor formation. Binding of ^{14}C-TCP to hepatic protein, DNA and RNA was found 4 hr after exposure to ^{14}C-TCP, intraperitoneally. During 1-48 hours post exposure, no significant change in ^{14}C-TCP bound to DNA was found, while binding to protein was maximal by 4 hr and decreased significantly by 48 hr. Binding to DNA and protein was cumulative after repeated doses. When TCP was analyzed for the generation of DNA cross-links, neither DNA-DNA or DNA-protein cross-links were detected (Weber and Sipes, 1991).

Acute Toxicity

Reported oral LD_{50} values for 1,2,3-TCP in rats range from 150 mg/kg (Albert 1982) to 500 mg/kg bw in Sprague-Dawley rats (Saito-Suzuki et al., 1982). Other reported values are 444 mg/kg 1,2,3-TCP for Carworth-Wistar male rats (Smyth et al., 1962).

In rats exposed to 1,2,3-TCP by oral gavage at 29, 59 and 118 mg/kg/day for 10 days, a significant increase in serum myocardial lactate dehydrogenase was observed in the high dose group (McKean et al., 1988). This finding was correlated with diffuse myocardial necrosis and degeneration, associated with a sub-acute inflammatory reaction. In heart cell cultures a faster beating rate was observed in doses from 0.1 mM to 2.5 mM 1,2,3-TCP.

In a combined acute and subchronic study, male and female Sprague-Dawley rats showed a cardiopathic response after a 10-day exposure to 118 mg/kg 1,2,3-TCP in corn oil. Toxicity was observed in the high dose group of both sexes of animals treated with 1.5, 7.4, 29 and 118 mg/kg/day for 10 days and 1.5, 7.4, 15 and 60 mg/kg for 90 days (Merrick et al., 1991). Weight gain suppression occurred at 118 mg/kg at the end of the 10-day study and at 60 mg/kg at the end of the 90-day study. The toxic histological finding was an inflammation-associated cardiopathy, including myocardial necrosis and degeneration with marked eosinophilia. When organ weights were normalized by body weight, liver and kidney values were generally increased relative to control in the highest dose groups of 10- and 90-day exposed rats. Thymic atrophy occurred in the 10 day exposed rats. 1,2,3-TCP was found to be the least toxic of the trihalogenated propanes in the induction of renal and testicular toxicity after intraperitoneal injection of the halogenated propane compounds into male Wistar rats (Lag et al., 1991). It showed very low potency as a nephrotoxicant and caused significant renal DNA damage only at high doses greater than 55 mg/kg.

Chronic Toxicity

No information was found on chronic toxic effects in humans from exposure to 1,2,3-TCP.

In a NTP study (1993), groups of male and female rats received 0, 3, 10 or 30 mg/kg 1,2,3-TCP in corn oil by gavage 5 d/wk up to 104 weeks. Up to 10 rats from each dose group were evaluated at 15 months. Absolute and relative liver and kidney weights of dosed rats were significantly greater than those of the controls. Chemical-related nonneoplastic lesions of the forestomach, oral mucosa, pancreas (males), kidney, mammary gland (females), preputial gland, and clitoral gland were observed in dosed rats. These effects included increased severity of nephropathy in male rats and increased incidences of basal cell and squamous hyperplasia of the forestomach (males and females), acinar hyperplasia of the pancreas (males), renal tubule hyperplasia, and preputial or clitoral gland hyperplasia in male and female rats.

Also in the NTP study, groups of male and female mice received 0, 6, 20 or 60 mg/kg 1,2,3-TCP in corn oil by gavage 5 d/wk for 104 weeks. Chemical-related nonneoplastic lesions included increased incidences of squamous hyperplasia of the forestomach and eosinophilic foci in the liver in male and female mice (NTP, 1993).

In a study for the NTP (1983), Hazelton Laboratories administered 1,2,3-TCP by gavage doses of 0, 8, 16, 32, 63, 125 or 250 mg/kg to rats and mice for 60 to 120 days, 5 days a week. Chemical-related findings were mortality at the 250 mg/kg dose in rats and mice and increased liver and kidney weights. Rats showed alterations in serum enzymes associated with renal and hepatic toxicity and decreased red cell mass. The highest no-observed-adverse-effect-level (NOAEL) was 8 mg/kg or 5.7 mg/kg/day, based on a 7-day week, in rats (IRIS, 1994). USEPA derived a reference dose of 6 ug/kg/day on the basis of this study.

In a study by Villeneuve (1985), groups of 10 male and 10 female weanling Sprague-Dawley rats were supplied drinking water containing 10, 100 or 1000 mg/L (1.5, 15, 150 mg/kg) 1,2,3-TCP for 13 weeks. Decreased growth rate was observed in both sexes receiving 150 mg/kg 1,2,3-TCP. Other effects were fatty livers, and elevation in serum cholesterol in female rats of the highest dose group. Hepatic aminopyrine demethylase and aniline hydroxylase were induced in male rats. The authors concluded the no-observed-effect-level (NOEL) was 100 mg/L (15 mg/kg bw/day).

In a study by Shell Oil (1993), with $B6C3F_1$ mice exposed to 8, 16, 32 , 63, 125 and 250 mg/kg/day 1,2,3-TCP in corn oil by gavage for 120 days, treatment-related deaths occurred at the highest level. At the 125 and 250 mg/kg/day dose levels, testicular and epididymal weights were decreased, liver weights and liver to bodyweight ratios were increased. Histological signs of liver toxicity, hyperkeratosis of the forestomach and regenerative bronchiolar epithelium were noted.

In a study by Biodynamics (1979), male and female rats were exposed to air concentrations of 0, 28, 93 or 304 mg/kg 1,2,3-TCP 6 hr/d, 5 d/wk for 13 weeks. Absolute and relative liver weights increased with treatment. Histological examination revealed treatment-related mild

centrilobular to midzonal hepatocellular hypertrophy, mild to marked peribronchiolar hyperplasia and mild to marked hematopoiesis in the spleen.

Reproductive and Developmental Effects

Gulati (1990) exposed male and female mice to 0, 30, 60 and 120 mg/kg 1,2,3-TCP by gavage for a 7-day pre-cohabitation and a 98-day cohabitation period in a continuous breeding protocol. The control and 120 mg/kg groups were later used in a cross-over mating trial to determine the sex affected by chemical treatment. The F_1 generation mice were also evaluated for developmental effects.

1,2,3-TCP caused a dose-related impairment of fertility (Gulati, 1990). In the high dose group, fewer pairs delivered third, fourth and fifth litters and litters had fewer live pups. Parental body weights were not decreased. In both male and female parental mice, liver weights were increased, female kidney and ovary weights were reduced. Testes and epididymal weights were slightly reduced in the high dose males. Sperm parameters were unchanged (NTP, 1983).

In the cross-over trial, treated females mated to control males produced fewer live pups (Gulati et al. 1990). These data suggest an impairment of female fertility. The fertility index in second generation pups fed 1,2,3-TCP was also significantly reduced. The number of pups was lower at the higher dose. There was a significant reduction in the proportion of male pups born alive in the 120 mg/kg group of the fifth litter. Gulati found clear evidence that 1,2,3-TCP at 120 mg/kg is a reproductive toxicant in Swiss mice. In contrast to other halogenated propanes, 1,2,3-TCP produced negative responses for the induction of dominant lethal mutations in male rats (Saito -Suzuki et al., 1982).

Genetic Toxicology

1,2,3-TCP was mutagenic in vitro in the presence of S9 metabolic activation. At two laboratories, positive responses were obtained for mutagenicity in Salmonella typhimurium strains TA97, TA98, TA100, and TA1535 in the presence of microsomal S9. No mutagenic activity was observed in TA1537, with or without S9 (NTP, 1993; Mahmood, 1988). Ratpan and Plaumann (1988) found that 1,2,3-TCP showed mutagenic activity in strains TA1535 and TA100 only with microsomal S9 activation. The activity was less than that for brominated analogs tribromopropane and 1,2-dibromo-3-chloropropane.

1,2,3-TCP induced gene mutation in L5178Y mouse lymphoma cells with, but not without, S9 (NTP, 1993; Shell, 1991). In cultured Chinese hamster ovary cells, sister chromatid exchanges and chromosomal aberrations were induced by 1,2,3-TCP. However, significant increases in the endpoints of both cytogenetic effects occurred only in the presence of S9 (NTP 1993). Von de Hude (1987) also found sister chromatid exchanges in Chinese hamster V79 cells activated with S9.

Weber and Sipes (1990) calculated a covalent binding index (CBI) in the liver of rats for

1,2,3-TCP that has been shown to roughly reflect the genotoxic potency of a chemical in long-term bioassays (Lutz, 1979). For 1,2,3-TCP the CBI ranged from 150 to 350, indicating a moderately genotoxic potential. In vitro studies using rat and human hepatic microsomes have shown that 1,2,3-TCP is bioactivated to 1,3-dichloroacetone (DCA) and 2,3-dichloropropanol. DCA was implicated as the major microsomal protein-binding metabolite. DCA is a direct acting mutagen (Weber and Sipes, 1992).

In hepatocyte cell culture assay of cell toxicity and DNA damage, Holmes et al. (1991) found 1,2,3-TCP is cytotoxic but does not significantly damage DNA compared to control cell cultures and structural analogs like 1,2-dibromo-3-chloropropane.

In the genotoxicity QSAR (quantitative structure-activity relationships) studies of Eriksson et al. (1991) based on activity in the DNA precipitation assay that estimates DNA damage in V79 Chinese hamster cells, 1,2,3-TCP was moderately active compared to a group of 58 saturated halogenated aliphatics. Ten of the compounds were used to construct the QSAR and six, including 1,2,3-TCP, were used to validate the model.

Glutathione (GSH) depletion studies showed that lack of GSH diminished DNA binding of 1,2,3-TCP. GSH appears to mediate the formation of reactive metabolites that can covalently bind to DNA (Volp et al., 1984). 1,2,3-TCP induced hepatic DNA damage (strand breaks) 1 hr after an intraperitoneal dose in a dose-dependent manner (Weber and Sipes, 1991).

Oncogenicity

There are no studies indicating oncogenic effects of 1,2,3-TCP in humans.

Oncogenic effects were induced in rats and mice after 1,2,3-TCP exposure. In a NTP (1993) bioassay, groups of male and female rats received 0, 3, 10 or 30 mg 1,2,3-TCP/kg bodyweight in corn oil by gavage, 5 d/wk up to 104 weeks. Survival of male and female rats receiving 10 or 30 mg/kg 1,2,3-TCP was significantly lower than controls. At 30 mg/kg, survival was markedly reduced due to chemical-related neoplasms. Final mean body weights of 30 mg/kg male and female rats were lower (13% and 12%, respectively) than those of controls.

Administration of 1,2,3-TCP to rats induced benign and malignant neoplasms of the oral mucosa (pharynx and tongue), forestomach, and preputial and clitoral glands; benign neoplasms of the exocrine pancreas and kidney in males; and malignant neoplasms of the mammary gland in females. The incidences of squamous cell papillomas and carcinomas of the oral mucosa were significantly increased in 10 and 30 mg/kg rats, while the incidences of squamous cell papillomas or carcinomas (combined) of the forestomach were significantly increased in all dosed groups. The incidence of pancreatic acinar adenoma was significantly increased in dosed males, but not in dosed females. Similarly, the incidence of adenoma of the kidney was significantly increased in 10 and 30 mg/kg male rats only. The incidences of adenoma or carcinoma (combined) of the preputial gland in

30 mg/kg males and of the clitoral gland in 10 and 30 mg/kg females (homologous organs) were significantly increased. The incidence of adenocarcinoma of the mammary gland was significantly increased in the 10 and 30 mg/kg females. The incidences of Zymbal's gland carcinomas were increased in 30 mg/kg males and females. Adenocarcinomas of the intestine occurred in small numbers of dosed rats and may have been chemical related. Under the conditions of these 2-year gavage studies, NTP concluded there was clear evidence of carcinogenic activity of 1,2,3-TCP in male and female F344/N rats.

Groups of male and female mice received 0, 6, 20, or 60 mg 1,2,3-TCP/kg body weight in corn oil by gavage 5 d/wk up to 104 weeks. The incidence of squamous cell carcinoma of the oral mucosa was significantly increased only in 60 mg/kg females. In contrast, the incidences of squamous cell papilloma and carcinoma of the forestomach were significantly increased in all groups of dosed mice. The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in all dosed groups of males and in 60 mg/kg females. The incidences of harderian gland adenoma were significantly increased in 20 mg/kg males and in 60 mg/kg males and females. The incidences of uterine adenoma, adenocarcinoma, and stromal polyp were significantly increased in 60 mg/kg females (NTP, 1993). Based on these results, NTP concluded there was clear evidence of carcinogenic activity of 1,2,3-TCP in male and female B6C3F_1 mice.

Survival rates of mice receiving 6, 20, or 60 mg/kg 1,2,3-TCP were also significantly lower than those of controls. Fina l mean body weights of 60 mg/kg males and females and 20 mg/kg males were lower (16%, 18% and 13%, respectively) than those of controls. Final mean body weights of 6 mg/kg males and females and 20 mg/kg females were similar to controls.

DERIVATION OF VALUE

1. Selection of Data

   The clear evidence of oncogenic activity at several sites after oral exposure in both sexes of rats and mice in a well-conducted bioassay (NTP, 1993) fulfills the definition of an oncogenic effect in 700.1 for 1,2,3-TCP. Therefore, a water quality value can be derived for 1,2,3-TCP using the section 702.4 procedure based on oncogenic effects.

   There are no human data on which to base a value.

   A summary of the data sets showing statistically and biologically significant increases in tumor response is presented in Table I. In rats, squamous cell carcinomas most often arise from large papillomas (Turusov and Mohr, 1990). Therefore, it is appropriate to combine the squamous cell carcinomas and papillomas of the oral cavity and forestomach in determining tumor incidence. The increasing trend in tumor incidence from lowest dose to highest is clear in the oral cavity, and there is a significant difference over controls in 10 mg/kg and 30 mg/kg

dose groups in male and female rats (NTP, 1993). Similarly, carcinomas and adenomas are combined in the clitoral and preputial glands and liver.

Incidences of squamous cell papillomas and carcinomas were significantly increased in the male and female rat forestomach from gavage treatments. The forestomach is a distention of the distal end of the esophagus (Dr. Elwell, personal communication). This phenomenon occurs in humans as well (Basmajian et al., 1982).

Based on the data for the oral cavity and forestomach in male and female rats in Table I, the oral cavity and forestomach are the most sensitive sites of the most sensitive species.

However, all data sets were used for calculations of animal dose to demonstrate the range of responses.

2. Selection of Model/Output

For derivation of a water quality standard, 6NYCRR Part 702 specifies use of a linear multistage (LMS) low-dose extrapolation model unless there is sufficient scientific evidence that supports use of another extrapolation procedure.

The GLOBAL82 LMS model (Crump, 1982) is chosen to estimate the dose associated with 10^{-6} excess cancer risk. Both the 95 percent lower confidence limit (LCL) and maximum likelihood estimate (MLE) are calculated by GLOBAL 82 for the animal dose associated with a 1×10^{-6} lifetime excess cancer risk (Table II). The confidence limit provides a value that is 95 percent certain not to exceed the value associated with the risk and is required by regulation. The MLE, when compared to the LCL, provides a measure of goodness-of-fit of the data.

Table I

Rates of Tumor Incidence in Mice and Rats
in NTP (1993) 1,2,3-TCP Carcinogenesis Bioassay

Dose mg/kg/day	Animal	Tumor Type	Tumor Incidence
0	male rats	oral cavity	1/50 (2%)
2.1		papilloma and	4/50 (8%)
7.1		carcinoma	19/49* (39%)
21.0			43/52* (83%)
0	female rats	oral cavity	1/50 (2%)
2.1		papilloma and	6/49 (12%)
7.1		carcinoma	28/52* (54%)
21.0			33/52* (63%)
0	male rats	forestomach	0/50 (0%)
2.1		papillomas	33/50* (66%)
7.1		carcinomas	42/49* (86%)
21.0			43/52* (83%)
0	female	forestomach	0/50 (0%)
2.1	rats	papillomas	16/49* (33%)
7.1		carcinomas	37/52* (71%)
21.0			19/52* (36%)
0	male rats	preputial	5/49 (10%)
2.1		gland	6/47 (13%)
7.1		adenomas and	8/49 (16%)
21.0		carcinomas	16/50* (32%)
0	female rats	clitoral	5/46 (11%)
2.1		gland	10/46 (22%)
7.1		adenomas and	17/50* (34%)
21.0		carcinomas	15/51* (29%)
0	female rats	mammary	1/50 (2%)
2.1		gland	6/49 (12%)
7.1		adenocarcinoma	12/52* (23%)
21.0			21/52* (40%)
0	male mice	hepatocellular	13/52 (25%)
4.3		adenoma	24/51* (39%)
14.		and	24/54* (44%)
43.		carcinoma	31/56* (55%)
0	female mice	hepatocellular	7/50 (14%)
4.3		adenoma	11/50 (22%)
14.		and	8/51 (16%)
43.		carcinoma	31/55* (56%)
0	female mice	oral cavity	0/50 (0%)
4.3		squamous	0/50 (0%)
14.		cell carcinoma	2/51 (4%)
43.			5/55* (9%)
0	female mice	uterus	0/50 (0%)
4.3		adenocarcinoma	7/50 (14%)
14.			5/51 (10%)
43.			9/55* (16%)

* Significant Increases

Table II. Animal Doses Associated with 10^{-6} Cancer Risk for 1,2,3-TCP

Data Set		Animal Dose ug/kg/day GLOBAL82 Output	
Animal	Tumor Site	95% LCL	MLE
male rat	forestomach	0.0046	0.0055
female rat	forestomach	0.014	0.016
male rat	oral cavity	0.013	0.023
female rat	oral cavity	0.013	0.016
male rat	preputial gland	0.048	0.110
female rat	clitoral gland	0.047	0.095
female rat	mammary gland	0.028	0.039
male mice	liver	0.057	0.098
female mice	liver	0.089	0.50
female mice	oral cavity	0.26	0.54
female mice	uterus	0.10	0.14

3. Conversions

The animal doses associated with a 1 x 10^{-6} excess cancer risk, are converted below to a human dose by the surface area conversion as specified in Part 702.

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

Human doses for all data sets are shown in Table III.

Human daily doses are converted to drinking water values that are based upon lifetime exposure of a 70 kg human consuming 2 liters of water per day.

4. Values and their Uncertainties

Results of the quantitative risk assessment based on male and female tumor incidence data from the NTP (1993) bioassay are presented in Tables II and III. Animal doses based on the lower confidence limit (LCL) of individual data sets range from 0.0046 ug/kg/day to 0.26 ug/kg/day for the various sites with increases in tumor incidences. The male rat forestomach is the most sensitive site in the most sensitive species according to these outputs from the LMS model. The occurrence of tumors was significant in both sexes 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 6 NYCRR Part 702 requirements as a basis for a value. The small differences between the MLEs and LCLs for the individual data suggest a good fit of data and a lower degree of uncertainty in predicting risk for the 10^{-6} level.

Table III. Human Doses Calculated from Animal Doses and Human Doses Converted to Water Values

Data Set			Human Dose ug/kg/day	Water Value ug/L
Sex/ Species	Tumor Site	Conversion Factor[1]	95% LCL	95% LCL
M rat	forestomach	0.18	8.3×10^{-4}	0.030
F rat	forestomach	0.16	2.2×10^{-3}	0.078
M rat	oral cavity	0.18	2.3×10^{-3}	0.082
F rat	oral cavity	0.16	2.1×10^{-3}	0.074
M rat	preputial gland	0.18	8.6×10^{-3}	0.30
F rat	clitoral gland	0.16	7.5×10^{-3}	0.26
F rat	mammary gland	0.16	4.5×10^{-3}	0.16
M mice	liver	0.085	4.8×10^{-3}	0.17
F mice	liver	0.084	7.5×10^{-3}	0.26
F mice	oral cavity	0.084	0.022	0.77
F mice	uterus	0.084	8.4×10^{-3}	0.30

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

where weight of male rats = 0.400 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

5. Selection of the Value

The most stringent value that can be derived from the procedures of 6 NYCRR Part 702 is 0.03 ug/L, based on oncogenic effects.

6. Other Values

Under the State Sanitary Code (10 NYCRR Part 5, Public Water Supplies), the New York State Department of Health has established a maximum contaminant level of 5 ug/L for "Principal Organic Contaminants" such as 1,2,3-TCP in drinking water.

ADJUSTMENT TO DERIVATION OF VALUE

The above value was derived in 1994 using an interspecies scaling of doses based on the

[2] USEPA, 1988.

2/3 power of relative body weights, as specified in 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 reevaluated from the male rat forestomach animal dose as follows:

$$\text{Human dose} = \left(\frac{0.40}{70}\right)^{0.25} (0.0046 \text{ ug/kg/day}) = 0.00126 \text{ ug/kg/day}$$

$$\text{Ambient water quality value} = \frac{(0.00126 \text{ ug/kg/day})(70/\text{kg})}{2 \text{ L/day}} = 0.0443 \text{ ug/L, rounded to } 0.04 \text{ ug/L}$$

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SEARCH STRATEGY

Integrated Risk Information System (IRIS) - Searched 1/94.

Registry of Toxic Effects of Chemical Substances (RTECS) - Searched 1/94.

Chemical Carcinogenesis Research Information System (CCRIS) - Searched 1/94.

TOXLINE - Searched by New York State Library for years 1977-1993.

National Technical Information (NTIS) - Searched by New York State Library for years 1977-1993.

BIOSIS - Searched by New York State Library for years 1977-1993.

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