PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

1,2,3-TRICHLOROPROPANE

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Public Health Goal for
1,2,3-Trichloropropane
in Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Branch
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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs are not regulatory requirements, but instead represent non-mandatory goals. Using the criteria described above, PHGs are developed for use by the California Department of Public Health (DPH) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Thus, PHGs are not developed as target levels for cleanup of ground or ambient surface water contamination, and may not be applicable for such purposes, given the regulatory mandates of other environmental programs.

Whereas PHGs are to be based solely on scientific and public health considerations, drinking water standards adopted by DPH are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DPH shall be set at a level that is as close as feasible to the corresponding PHG, with emphasis on the protection of public health. Each primary drinking standard adopted by DPH is required to be set at a level that is as close as feasible to the corresponding PHG, with emphasis on the protection of public health. MCLs established by DPH must be at least as stringent as the federal MCL, if one exists.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR 1,2,3-TRICHLOROPROPANE IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 0.0007 microgram/liter (µg/L), or 0.0007 parts per billion (ppb) for 1,2,3-trichloropropane (1,2,3-TCP). The PHG is based on carcinogenic effects observed in animals (NTP, 1993). Significant increases in tumors have been observed in a number of tissues in male and female mice and rats administered 1,2,3-TCP by the oral route. 1,2,3-TCP was genotoxic in studies *in vivo* and *in vitro*. DNA adducts have been observed in animals following exposure to 1,2,3-TCP. Studies of 1,2,3-TCP metabolism, while incomplete, link 1,2,3-TCP genotoxic and carcinogenic activity with metabolism to a reactive form of the chemical. Evidence that links exposure to 1,2,3-TCP to an increased incidence of cancer in humans is lacking.

Cancer potency was calculated from tumors at various sites in male and female rats and mice given chronic oral doses of 1,2,3-TCP. Tumors in the female mouse forestomach yielded the lowest lower-bound estimate of the dose associated with a 10 percent increased incidence of tumors, and therefore this effect was used to estimate cancer potency. According to the International Agency for Research on Cancer (IARC, 2003), "carcinogens that are DNA-reactive and cause forestomach tumors in rodents -- even if they only caused tumors at this site -- should be evaluated as if they presented a carcinogenic hazard to humans."

For our evaluation, a time-to-tumor model was employed, which takes into consideration the time tumors were first observed as well as the number of tumors. An upper bound estimate of cancer potency for 1,2,3-TCP of 25 $(mg/kg\text{-}day)^{-1}$ was derived using the lower 95^{th} percent confidence limit on the dose associated with a 10 percent increased incidence of forestomach tumors and an assumed linear relationship between dose and response at low doses. The PHG was derived employing this cancer potency and exposure to 4 liter-equivalents (L_{eq}) per day of water, representing the combined exposures by oral, inhalation, and dermal routes.

A health protective level was also derived based on non-carcinogenic effects. A no observed adverse effect level (NOAEL) of 8 mg/kg-day at 8 and 17 weeks was identified from a 17 week subchronic gavage study, based on decreased erythrocyte mass (lower mean hematocrit, hemoglobin and erythrocyte counts) at doses of 16 mg/kg-day or greater in female rats. A health protective level of 0.08 mg/L or 80 ppb was derived employing an uncertainty factor of 1,000, and the ingestion of 4 L_{eq}/day of water.

There is no California or federal Maximum Contaminant Level (MCL) for 1,2,3-TCP. The California Notification Level for 1,2,3-TCP is set at 0.005 µg/L, the detection limit for the purposes of reporting (DLR). Notification levels are health-based advisory levels established by California Department of Public Health (DPH, formerly the Department of Health Services [DHS]) for chemicals in drinking water that lack MCLs. DPH advises,

"If a chemical concentration is greater than its notification level in drinking water that is provided to consumers, CDPH recommends that the utility inform its customers and consumers about the presence of the chemical, and about health concerns associated with exposure to it"
(http://www.cdph.ca.gov/certlic/drinkingwater/Pages/NotificationLevels.aspx).

INTRODUCTION

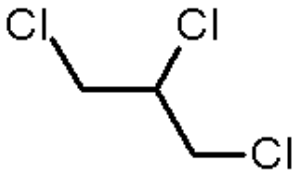
The purpose of this document is to develop a PHG for 1,2,3-TCP. PHGs are based on a comprehensive analysis of information on the toxicology of the compounds. PHGs are based solely on protection of public health without regard to cost impacts or other factors, as specified the California Safe Drinking Water Act (HSC 116350 et seq.). OEHHA sets PHGs for carcinogens at a *de minimis* risk level of one in a million (10^{-6}), assuming a lifetime of exposure to the chemical in the drinking water. PHGs for non-carcinogens are based on levels estimated to be without risk of any adverse effects for exposures up to a lifetime, to the general population as well as any significant identifiable sensitive subpopulations.

A PHG for 1,2,3-TCP has been developed by OEHHA at the request of the California DPH, because of repeated detections of this chemical in California drinking water sources. The major source of the 1,2,3-TCP is presumably leaching from hazardous waste sites (DHS, 2005). This chemical is listed on the priority list of hazardous substances maintained by the federal Agency for Toxic Substances and Disease Registry (ATSDR, 2005). 1,2,3-TCP has been reported to cause cancer in laboratory animals (U.S. EPA, 1997), which is the basis for the DPH notification level of 0.005 μg/L (DHS, 2005). It was also listed in 1992 as known to the State of California to cause cancer (Title 27, California Code of Regulations, Section 27001) and has been identified as reasonably anticipated to be a human carcinogen by the National Toxicology Program (NTP, 2004).

Available scientific information on 1,2,3-TCP was identified using U.S. EPA's Integrated Risk Information System (IRIS), PubMed, and other relevant reference databases. Two reviews were identified and were particularly useful in identifying and evaluating relevant toxicity studies (WHO, 2003; ATSDR, 1992). There is no California or federal MCL for 1,2,3-TCP.

Chemical Identity

1,2,3-Trichloropropane is also known as allyl trichloride, trichlorohydrin, and glycerol trichlorohydrin. The structure of 1,2,3-TCP is shown below (WHO, 2003).



The physical and chemical properties of 1,2,3-TCP are summarized in Table 1.

Table 1. Physical and Chemical Properties of 1,2,3-Trichloropropane[1]

Property	**Value**
CAS No.	96-18-4
Physical state	Liquid
Molecular weight	147.43
Density	1.3888 g/cm^3 at 20° C; 1.38 g/cm^3 at 20° C
Solubility in water	1.75 g/L at 20° C; 1.75 g/L at 25° C
Solubility in organic solvents	Soluble in ethyl alcohol, chloroform, ethyl ether, benzene
Vapor Pressure	3.1, 3.69 mm Hg at 25° C; 0.492 kPa at 25° C
Henry's Law constant	3.17; 3.43 x 10^{-4} atm-m^3/mol at 25° C 22.83 x 10^{-4} Pa-m^3/mol at 25° C 0.013 dimensionless (K_{aw})
Absorption to organic carbon (Koc) Log (Koc)	77 to 95 1.98
Octanol-water partition coefficient (Log K_{ow})	1.99; 2.54; 2.27
Conversion factor:	1 ppm = 6.1 mg/m^3 at 20° C, 101.3 kPA 1 mg/m^3 = 0.16 ppm

[1]From ATSDR, 1992; WHO, 2003; HSDB, 2005.

Production and Uses

1,2,3-Trichloropropane has been used as a solvent and degreasing agent and in the synthesis of other compounds such as epichlorohydrin and certain polymers (WHO, 2003; NTP, 2004). The continued use of 1,2,3-TCP as a solvent is unclear. The Toxic Substances Control Act (TSCA) Inventory Update lists usage in 2002 as >1 to 10 million pounds, which is a decrease in usage from earlier reporting periods (U.S. EPA, 2007a). 1,2,3-TCP also occurs as a byproduct in the production of chemicals (propylene, chlorohydrin, dichlorohydrin, epichlorohydrin and certain pesticides (dichloropropene (Telone II)) (NTP, 2004).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Because of the relatively high volatility of 1,2,3-TCP, it will be readily transferred into air. Low levels of 1,2,3-TCP (<1 μg/m^3) have been detected in ambient air in some studies but not in others (reviewed by WHO, 2003). Much higher levels were detected in ambient air in Kuwait (mean 491 μg/m^3 from 19 samples) than in other areas sampled. 1**,**2**,**3-Trichloropropane will react with hydroxyl radicals in the atmosphere, with an estimated half-life of 46 days (HSDB, 2005). Because of its high water solubility, 1**,**2**,**3-TCP can also be removed from the atmosphere by rain. The combination of volatilization, washout, and resistance to degradation may result in recycling of 1**,**2**,**3-TCP among the environmental compartments (HSDB, 2005).

Soil

Low levels of 1,2,3-TCP have been detected in soil at some hazardous waste sites (ATSDR, 1992). Its detection in groundwater near hazardous waste sites implies limited adsorption to soils (high mobility) and a low rate of biodegradation in soil and groundwater (HSDB, 2005). A WHO review cites limited reports of detection of 1,2,3-TCP in groundwater after use of a nematocide containing 1,2,3-TCP (WHO, 2003).

Water

As discussed by HSDB (2005), 1**,**2**,**3-TCP should readily volatilize from surface water because of its high Henry's Law constant. Its half-life was estimated to be 6.7 hours in a river and 5.7 days in a lake (HSDB, 2005). Due to its low adsorptivity, it should not be substantially adsorbed to sediment or particulates in the water column. 1**,**2**,**3-Trichloropropane is resistant to biodegradation and hydrolysis, so breakdown is not expected to be an important fate process in the aquatic environment. Also, according to HSDB (2005), it would not be expected to bioconcentrate in aquatic organisms.

The distribution of peak concentrations of 1,2,3-TCP in water sources in California as of 2005 is shown in Table 2. 1,2,3-TCP detections in drinking water sources (two or more times) reported by the California DPH in 2006 are shown in Table 3.

Table 2. Distribution of Peak Concentrations of 1,2,3-TCP Detected in California Drinking Water Sources*

Peak concentrations of 1,2,3-TCP		
Peak (μg/L)	**No. of sources**	**% of detects**
>50	1	-
5.1 – 50	4	2
0.51 - 5.0	17	7

0.051 – 0.5	91	35
0.0051 – 0.05	146	56
<0.0051	1	-
TOTAL	**260**	**100**

*From DHS, 2005. "Sources" includes active, standby, inactive, and abandoned or destroyed sources, and may include both raw and treated drinking water wells and surface water sources, distribution systems, blending reservoirs, and other sampled entities.

Table 3. Sources Reporting 1,2,3-TCP Detections and Their Peak Concentrations*

County	TOTAL Sources	<0.0051 µg/L	0.0051 - 0.05 µg/L	0.051 - 0.5 µg/L	0.51 - 5.0 µg/L	5.1 - 50 µg/L	>50 µg/L	No. of Systems
Kern	96	1	40	51	4	.	.	18
Fresno	43	.	31	10	2	.	.	8
Los Angeles	41	.	25	10	3	2	1	15
Tulare	26	.	19	5	1	1	.	5
Merced	23	.	8	9	6	.	.	10
San Bernardino	22	.	17	4	1	.	.	6
Riverside	18	.	14	4	.	.	.	6
San Joaquin	8	.	4	4	.	.	.	2
San Diego	7	.	3	2	2	.	.	2
San Mateo	7	.	3	3	1	.	.	2
Stanislaus	6	.	4	2	.	.	.	5
Monterey	2	1	.	1	.	.	.	2
Solano	1	.	.	.	1		.	1
Sacramento	1	.	.	1	.	.	.	1
Kings	1	.	1	.	.	.	.	1
Madera	1	.	1	.	.	.	.	1
TOTAL	**303**	**2**	**171**	**104**	**20**	**4**	**1**	**85**

* Sources with two or more reported 1,2,3-TCP detections (DHS, 2008). "Sources" includes active, standby, inactive, and abandoned or destroyed sources, and may include both raw and treated drinking water wells and surface water sources, distribution systems, blending reservoirs, and other sampled entities.

Food

No data were located on food analyses or content of 1,2,3-TCP.

Exposure

Studies of human exposure to volatile chemicals in drinking water, including radon and trihalomethanes indicate that in addition to ingestion, inhalation exposure (from chemical volatilized from showering and other indoor activities) and dermal exposure can significantly contribute to the overall daily intake (Jo *et al*. 1990a,b; McKone, 1987; Nieuwenhuijsen *et al*., 2000; McKone and Layton, 1986). U.S. EPA (1991) also suggested this in a guidance memorandum from its Risk Assessment Forum: "Exposure to volatile organic compounds in tap water during showering has been found to be approximately equivalent, within an order of magnitude (i.e., plus or minus a factor of three), to exposure from ingesting two liters per day of the same water."

The CalTOX multimedia exposure model (DTSC, 1994) was employed to determine if inhalation and dermal exposures to 1,2,3-trichloropropane during showering and other activities in the household substantially added to the daily exposure to 1,2,3-trichloropropane due to ingestion. CalTOX is a seven-compartment regional and dynamic fugacity model in a Microsoft Excel format. The chemical parameters for 1,2,3-trichloropropane used in CalTOX were: MW 147, Kow 178, Tm (K) 258.4, VP (Pa) 496, S (mol/m^3) 12.9, and H ($Pa\text{-}m^3/mol$) 38.5. Kp (dermal transfer coefficient) of 0.01 cm/hr was estimated based on Kow and molecular weight (U.S. EPA, 1992; Potts and Guy, 1992).

Human parameters were set for a 70 kg average human consuming 2.0 L/day of tap water (0.028 L/kg-day). The vadose zone soil compartment was loaded with various concentrations of 1,2,3-trichloropropane and the model was run to determine average in-house exposures by different exposure routes. Since the model predicts exposure rather than absorbed dose, the inhalation pathway values were adjusted to assume 50 percent absorption of 1,2,3-trichloropropane at low environmental concentrations while ingested 1,2,3-trichloropropane was assumed to be 100 percent absorbed at low doses.

Dermal exposure was estimated to contribute less than 2 percent of the overall exposure. CalTOX predicted that inhalation exposure was essentially equivalent to exposure due to the ingestion of drinking water, which is consistent with values derived by various techniques for other VOCs. Given that drinking water exposure of an adult is assumed to be 2 L/day, the added exposure from the inhalation pathway based on the findings of CalTOX is 2 Leq/day for a total of 4 Leq/day. The calculation of the PHG will be based on exposure to 4 L_{eq} of water/ day.

METABOLISM AND PHARMACOKINETICS

Absorption/Distribution/Elimination

Radiolabeled [1,3-^{14}C]-1,,2,3-trichloropropane (3.6 mg/kg) was administered to F-344 rats (three rats per time point) by injection into the tail vein (Volp *et al*., 1984). Levels of radioactivity were measured in excreta to study 1,2,3-TCP elimination. The animals were sacrificed at various times and tissue samples collected. In a separate study, rats were anesthetized and the bile duct was cannulated to determine the amount of 1,2,3-TCP excreted into the bile.

1,2,3-TCP was rapidly distributed in the rat with 70 percent of the dose accounted for in adipose tissue, skin and muscle after 15 minutes. After 4 hours, the amount of 1,2,3-TCP in the liver was larger than the amount of 1,2,3-TCP in adipose tissue, skin and muscle. The amount in the small intestine increased to over nine percent of the administered dose after one hour.

Radioactivity was excreted by three routes, in the urine, feces and expired air. By 24 hours, nearly 90 percent of 1,2,3-TCP was recovered in excreta, 40 percent of the dose was accounted for in the urine, 18 percent in the feces and 30 percent in expired air. More than 99 percent of the dose was recovered by day six with 47 percent of the dose recovered in the urine. Five percent of the dose in expired air was recovered unchanged while 25 percent of the administered dose was recovered as carbon dioxide. Little of the dose was recovered unchanged in the urine and feces.

Overall, approximately 30 percent of the dose was excreted in the bile while only 18 percent was recovered in the feces, suggesting some reabsorption of biliary metabolites from the intestine. The maximum rate of biliary excretion occurred at 1 to 1.5 hours post-administration. Administration of glycidol, which decreased hepatic glutathione levels, reduced biliary excretion to only 16 to 30 percent of the rate in control animals. These findings by Volp *et al*. (1984) suggested that conjugation with glutathione is an important element in 1,2,3-TCP metabolism.

Radiolabeled 1,2,3-trichloropropane was administered in corn oil to male and female rats and male mice by gavage. Rats were administered 30 mg/kg, while mice were administered either 30 or 60 mg/kg (Mahmood *et al*., 1991). These doses were selected because they were employed in the NTP cancer bioassay (NTP, 1993).

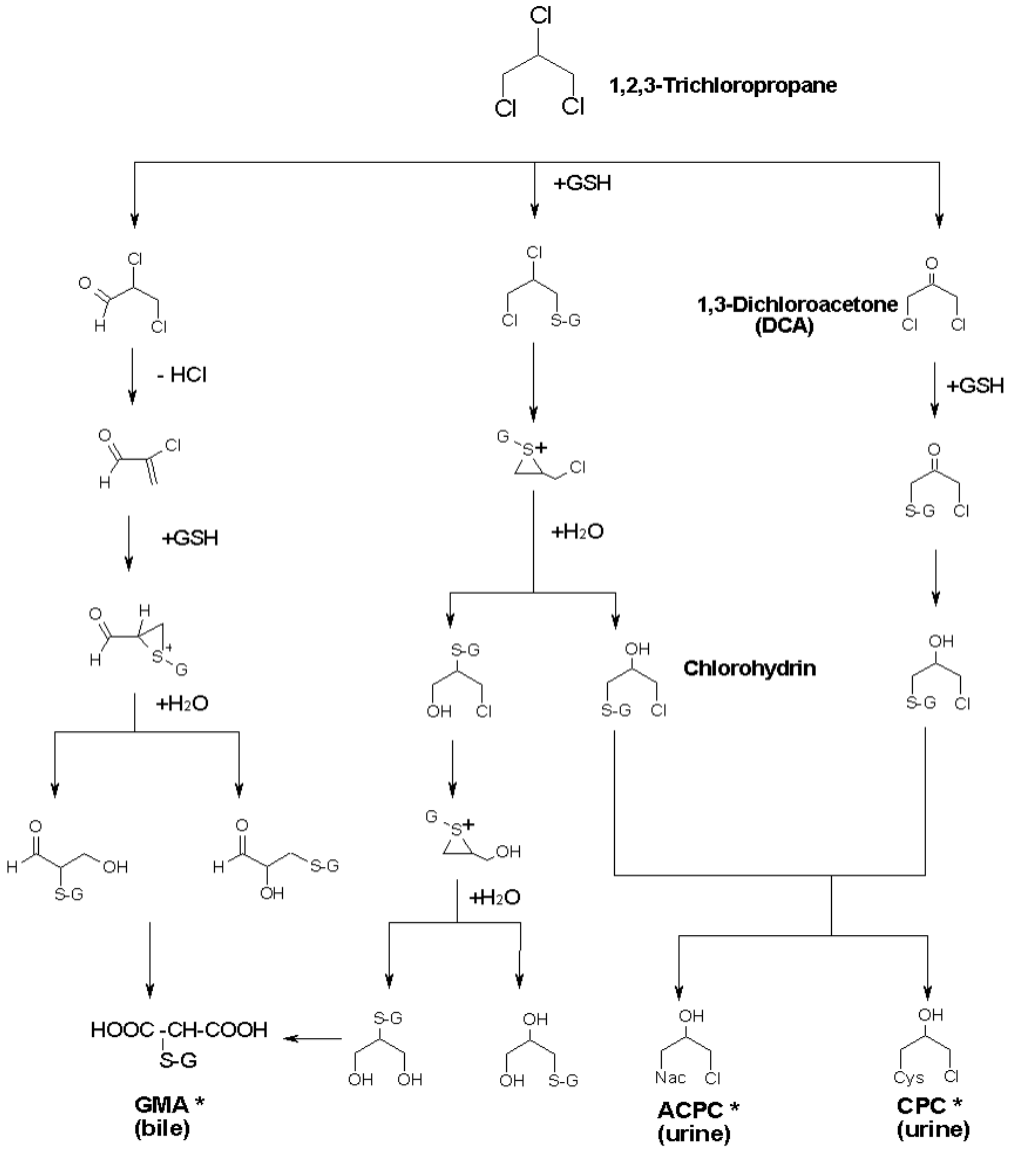
Similar to the study of Volp *et al*. (1984), 1,2,3-TCP was initially distributed in the rat (6 hours post-administration) to the adipose tissue, liver and kidney. Levels of 1,2,3-TCP in adipose tissues were markedly lower by 24 and 60 hours post administration while levels in the liver and kidney remained elevated. Less than 50 percent of the radioactivity remaining in the forestomach, liver and kidney was extractable in solvents at 24 and 60 hours post-administration, suggesting that it was covalently bound to macromolecules. There were little differences in the levels in male and female rats. Radioactivity levels in the rat tissues were substantially higher than in the mouse tissues. The radioactivity levels in mouse tissue were below those in the rat even when twice the dose was administered to the mice.

Metabolism

The metabolism of 1,2,3-TCP is not fully understood. Various metabolic pathways have been proposed (Figure 1) based on recovered metabolites and what is known about the metabolism of similar molecules such as dibromochloropropane (Mahmood *et al*., 1991; Weber and Sipes, 1992). Metabolism appears to involve cytochrome P-450 and glutathione.

1,2,3-TCP was rapidly metabolized in both the mouse and rat. More than half of the dose was recovered in excreta within 24 hours. Metabolism, measured by the amount of CO_2 collected in expired air, was more rapid in the male mouse than in the male rat during the first 24 hours. Doubling of the dose in the mouse did not alter the pattern of excretion in the mouse, indicating that metabolism did not appear to be saturated. Over 50 percent of the radioactivity was recovered in the urine (50 to 57 percent in the rat and 65 percent in the mouse) with 15 to 20 percent of the administered dose recovered in expired air and feces. Expired volatiles represented approximately 2 percent of the administered dose.

Figure 1. Proposed metabolic pathways of 1,2,3-Trichloropropane[1]



ACPC = *N*-acetyl-*S*-(3-chloro-2-hydroxypropyl)-L-cysteine
CPC = *S*-(3-chloro-2-hydroxypropyl)-L-cysteine
GMA = 2-(*S*-glutathionyl)malonic acid
S-G = S-glutathione
GSH = Reduced glutathione
Nac = N-acetyl-L-cysteine
Cys = L-cysteine

[1]From WHO, 2003; Mahmood *et al.*, 1991.

One metabolite, N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine was identified as the major metabolite in the urine of rats but was a minor constituent in mouse urine, representing 40 percent of urinary radioactivity in the rat and only 3 percent in the mouse at six hours. S-(3-chloro-2-hydroxpropyl)cysteine was the other major constituent in rat urine. These metabolites indicate the involvement of glutathione and also suggest the formation of reactive intermediates that are consistent with the observed unextracted (covalently bound) radioactivity in the tissues.

DNA, RNA and protein were extracted from the liver of male F-344 rats at various times after radiolabeled 1,2,3-TCP was administered i.p. in vegetable oil (30 mg/kg) (Weber and Sipes, 1990). Radioactivity was covalently bound to the protein, DNA and RNA fractions. Inducers of drug metabolism, phenobarbital or beta-naphthoflavone, reduced (phenobarbital) or had no effect (beta-naphthoflavone) on the labeling of protein or DNA. Administration of SKF 525-A, an inhibitor of cytochrome P-450 metabolism, produced an increase in labeling compared to the untreated control group. Administration of an agent than reduces the level of glutathione in the liver (L-buthionine-(S,R)-sulfoximine) resulted in a marked increase of binding of radioactivity to proteins and a marked reduction of binding to DNA, suggesting an important role for glutathione in 1,2,3-TCP activation.

Given that activation of 1,2,3-TCP appears necessary for its mutagenic activity, agents that stimulate drug metabolism might be expected to increase the binding of 1,2,3-TCP metabolites to macromolecules. However, induction of cytochrome P450 reduced the amount of binding to DNA, and blocking metabolism by cytochrome P450 with SKF 525-A increased DNA binding. The authors suggest that different forms of cytochrome P450 may shunt TCP into metabolic pathways that produce metabolites that do not bind to DNA. A reduction of cellular glutathione levels that resulted in reduced binding of 1,2,3-TCP to DNA suggests that glutathione is involved in the activation of 1,2,3-TCP.

1,2,3-TCP metabolism was investigated *in vitro* in microsomal and cytosol preparations from human and male F-344 rat livers (Weber and Sipes, 1992). In the rat, 1,2,3-TCP was metabolized to 1,3-dichloroacetone (DCA) in the presence of microsomal protein and a NADPH generating system. The investigators noted that DCA is a direct-acting mutagen and may be responsible for the mutagenic and carcinogenic activity associated with 1,2,3-TCP. The rate of DCA formation in rat liver microsomes was approximately 10 times that using microsomes prepared from human livers.

Pretreatment of rats with phenobarbital and dexamethasone, inducers of cytochrome P450, substantially increased the rate of metabolism, while adding a cytochrome P450 inhibitor; SKF 525-A, to the incubations markedly reduced the rate of metabolism. Incubation of 1,2,3-TCP with rat microsomes resulted in the formation of reactive species that were covalently bound to the microsomal proteins. As expected, the pretreatment of rats with inducers of cytochrome P450 markedly increased binding to microsomal protein. Interestingly, induction of cytochrome P450 resulted in increased binding to microsomal protein *in vitro* in this study, while binding to DNA *in vivo* was decreased by the inducer of cytochrome P450 (Weber and Sipes, 1990). Thus it is unclear whether the lower rate of metabolism in the human liver observed *in vitro* would be reflected in an

increase or decreased binding of 1,2,3-TCP metabolite(s) to DNA in human liver relative to the rat liver.

Little binding occurred when a NADPH generating system was omitted from the *in vitro* system. Addition of 1,2,3-TCP to a cytosol fraction did not yield reactive species that covalently bound to cytosol proteins. Addition of glutathione to the microsomes inhibited the binding, even in the absence of glutathione-S-transferase. These findings indicate that reactive species of 1,2,3-TCP produced by cytochrome P450 are reacting with glutathione.

The addition of alcohol dehydrogenase and NADH to the microsomes yielded mostly 1,3-dichloro-2-propanol, and some 2,3-dichloropropanol. This finding suggests the formation of a reactive intermediate *in vivo* (converted to alcohols by the addition of alcohol dehydrogenase in this *in vitro* system) that is normally difficult to detect because it rapidly binds to large macromolecules such as microsomal proteins (Weber and Sipes, 1990, 1992).

To summarize, as shown in Table 1, 1,2,3-TCP metabolism is complex. Several pathways that involve cytochrome P450 mono-oxygenases and glutathione mediated metabolism have been identified. The various pathways produce active metabolites that bind to proteins and DNA. Agents that change the activity of these xenobiotic metabolizing enzymes may increase or decrease 1,2,3-TCP binding to proteins and DNA, suggesting competing reactions.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Oral LD_{50}s ranging from 150 mg/kg to 500 mg/kg have been reported in the rat (reviewed by ATSDR, 1992; WHO, 2003).

Subchronic Toxicity

Exposure of mice to 1,2,3-TCP at 1 to 130 parts per million (ppm) by inhalation for less than two weeks resulted in irritation of the eye and nose, decreased thickness of olfactory epithelium, and increased liver weight (reviewed by ATSDR, 1992; WHO, 2003).

Male and female Sprague-Dawley rats (10 animals/group) were administered 1,2,3-TCP at 0, 10, 100, or 1,000 ppm in drinking water for 90 days (Villeneuve *et al*. 1985). The authors reported only the amount of chemical ingested (based on measured water intake and weight gain) for high dose males (113 mg/kg-day) and the two highest female dose groups (17.6 and 149 mg/kg-day, respectively). Both body weights and water intakes were reduced in male and female rats in the high-dose group.

Liver and kidney weights relative to body weight were elevated in high-dose males and the two highest-dose groups in females. Brain weight relative to body weight also was

elevated in the high-dose group. Some of these findings appear to reflect a loss in body weight, as the average organ weights were essentially unchanged in the treatment groups. Indicators of hepatic effects such as serum cholesterol levels, serum hepatic aniline hydroxylase activity and/or aminopyrine demethylase active were elevated, particularly in males and in the high-dose groups. Certain hematological changes were noted but the investigators reported that the levels were considered to be in the normal range. Histological changes were observed in the liver, kidney, and thyroid. Changes were mild and were most evident in the highest-dose groups. The authors concluded that 1,2,3-TCP did not cause overt toxicity in this study.

1,2,3-TCP was administered in corn oil by gavage to male and female Sprague-Dawley rats at 0, 1.5, 7.4, 29.5, 118 mg/kg-day for 10 days or 0, 1.5, 7.4, 14.7, 59 mg/kg-day for 90 days (Merrick *et al*., 1991). Final body weights were significantly decreased in male and female rats in the high dose groups after 10 or 90 days of exposure. The weights of the brain, testis, kidney, and liver were elevated relative to body weight in the high-dose groups, which probably reflected a lower body weight compared to control. The most notable toxicity in these animals was a diffuse inflammation-related necrosis of the heart. The inflammation was more pronounced at higher doses and after 90 days of exposure. Males appeared to be more sensitive than females. Effects of 1,2,3-TCP on other tissues appeared to be minimal, transient (thymus), or were also observed in the control group (liver, male rats).

Male and female CD rats were exposed to 1,2,3-TCP by inhalation, 6 hours/day five days/week (Johannsen *et al*., 1988). Animals were exposed to 0, 100, 300, 600 and 900 ppm in a four-week pilot study and 0, 5, 15 and 50 ppm or 0, 0.5, 1.5 ppm in a followup 13-week study. In the four-week study, nine out of ten rats died with a single exposure to 900 ppm, while three out of 10 rats died that received 600 ppm and 1 out of ten rats died at 300 ppm. A dose dependent reduction in body weight and an increase in liver/body weight ratios in all treatment groups were noted. Effects on ovary, spleen, kidney and testis weights were also observed.

In the 13-week study, no treatment-related deaths occurred. The body weights of female rats exposed to 15 and 50 ppm of 1,2,3-TCP were significantly lower than control after two weeks of exposure. No biologically significant effects on hematology or clinical chemistry were observed in male or female rats. Effects on absolute or relative liver weights were observed in rats exposed to 5, 15 or 50 ppm. Mild histopathology was reported in the lungs (male and female), liver (male) and spleen (female; mild to marked) in rats exposed to 5, 15 or 50 ppm. Midzonal hepatocellular hypertrophy was observed in the livers of male rats exposed to 15 or 50 ppm. No treatment-related histopathology was observed at lower concentrations.

In a study designed to select doses for a two-year cancer bioassay, 1,2,3-TCP was administered (0, 8, 16, 32, 63, 125, 250 mg/kg-day) in corn oil by gavage, 5 days per week to male and female F-344 rats and B6C3F_1 mice for 17 weeks with an 8-week interim evaluation (NTP, 1993; WHO, 2003). Rats appeared to be more sensitive to 1,2,3-TCP than mice. All male and female rats that received 250 mg/kg-day died and four of 10 females and one male rat that received 125 mg/kg-day died during the study.

Mean body weight of male rats receiving 63 or 125 mg/kg-day and female rats receiving 125 mg/kg-day were significantly decreased.

Absolute and relative liver weights were significantly greater than control in male rats receiving 32 mg/kg-day or greater and in female rats receiving 16 mg/kg-day or greater. Hepatocellular necrosis was evident in female rats receiving 125 mg/kg-day. Absolute and relative kidney weights of male rats receiving 32 mg/kg-day or more or female rats receiving 63 mg/kg-day or more were significantly increased over control. Regenerative hyperplasia in the kidney was observed in the kidney of male and female rats receiving 64 mg/kg-day at 8 weeks. Decreased erythrocyte mass (lower mean hematocrit, hemoglobin and erythrocyte counts) were observed at doses of 16 mg/kg-day or greater at 8 and 17 weeks in female rats and 16 mg/kg-day or greater at 8 weeks and 63 mg/kg-day or greater at 17 weeks in male rats.

Clinical chemistry findings were consistent with the aforementioned changes in the liver, with female rats that received 125 mg/kg-day exhibiting prominent increases in serum alanine aminotransferase, aspartate aminotransferase and sorbitol dehydrogenase activity. Bilirubin levels were elevated in males and females receiving 63 and 125 mg/kg-day. Effects on erythrocytes in mice were observed at 63 mg/kg-day in male mice and 16 mg/kg-day in female mice (significant decreases in hematocrit and erythrocyte levels at 8 weeks in male mice and 16 weeks in female mice). Effects on the liver in mice were also observed but at higher doses than in rats. Significant increases in serum enzymes that are indicative of liver toxicity were not observed in mice.

Genetic Toxicity

In *in vitro* bioassays, 1,2,3-TCP was generally positive for genotoxic activity in the presence of metabolic activation and negative without metabolic activation. Results of NTP genotoxicity studies where 1,2,3-TCP was tested in various strain of *S. typhimurium* were generally positive (NTP, 1993). 1,2,3-Trichloropropane was also positive with metabolic activation, in inducing gene mutations in mouse lymphoma cells, sister chromatid exchange in CHO and V79 cells, chromosomal aberrations in CHO cells, and micronuclei in human lymphoblast cell lines but did not induce unscheduled DNA synthesis in primary rat hepatocytes (WHO, 2003).

1,2,3-TCP was negative in a micronucleus assay with or without added S9 mix in isolated human lymphocytes (Tafazoli and Kirsch-Volders, 1996). In isolated human lymphocytes, the toxicant was positive in an alkaline single cell gel electrophoresis test (comet assay) indicating its ability to cause DNA breaks with and without added S9 mix (Tafazoli and Kirsch-Volders, 1996).

In vivo genotoxicity studies with 1,2,3-TCP revealed DNA single strand breaks in rat liver (Weber and Sipes, 1991). Other tests described below demonstrated the formation of DNA adducts following 1,2,3-TCP administration. DNA adduct formation was investigated in male F-344 rats and male B6C3F$_1$ mice administered 1,2,3-TCP in corn oil by gavage at the highest doses and one-tenth the doses administered in the NTP bioassay (La *et al*., 1995). DNA was isolated from various tissues and adducts were

isolated by HPLC. In a separate study, 1,2,3-TCP was administered by intravenous injection to increase adduct formation in the liver so that adducts could be identified.

One DNA adduct predominated in the liver, S-[1-(hydroxymethyl)-2-(N7-guanyl)ethyl]glutathione. DNA adducts were detected in a number of tissues including tissues where tumors were observed in the NTP study. Adducts were also detected in tissues where tumors were not observed, sometimes at very high levels, e.g., in glandular stomach in rats and mice. The lack of close concordance between adduct formation and the sites of the tumors suggests that other factors are involved in tumorigenesis.

The effect of vehicle and route of administration on DNA adduct formation was investigated in male $B6C3F_1$ mice administered 6 mg/kg-day radiolabeled 1,2,3-TCP for five days either by gavage or in drinking water (La *et al*., 1996). DNA from the forestomach and liver (target tissues in NTP cancer bioassay) and glandular stomach and the kidney (non-target tissues) was isolated and adducts were characterized. The S-[1-(hydroxymethyl)-2-(N7-guanyl)ethyl]glutathione DNA adduct appeared to predominate in all tissues.

Statistically significant increased adduct levels were detected in kidney and liver but not the glandular stomach or the forestomach when 1,2,3-TCP was administered in corn oil compared to a drinking water vehicle. Statistically significant increases in cell proliferation were not observed in any of the four tissues when 1,2,3-TCP was administered in drinking water. In contrast, statistically significant increased cell proliferation was observed in all four tissues when 1,2,3-TCP was administered in corn oil. The changes in adduct formation and cell proliferation occurred in tissues with a tumorigenic response in the NTP bioassay (liver and forestomach) as well as tissues where no response was detected (glandular stomach and kidney). In this study, neither adduct formation nor cell proliferation appeared to be predictive of the tumorigenic response observed in the NTP bioassay.

Ito and coworkers investigated the relevance of the predominant DNA adduct (S-[1-(hydroxymethyl)-2-(N7-guanyl)ethyl]glutathione) on ras gene mutations in forestomach tumors from mice administered 1,2,3-TCP (Ito *et al*., 1996). Specific gene mutations were observed in tissue samples from forestomach tumors obtained from the NTP (1993) cancer bioassay. Tumors in ten of sixteen mice had mutations in the H-*ras* or K-*ras* gene. The observed AT to TA or GC to CG transversions were not consistent with miscoding properties of the (S-[1-(hydroxymethyl)-2-(N7-guanyl)ethyl]glutathione) adduct suggesting other adducts or additional mechanism(s) were involved in the pathogenesis of the tumors.

The available studies (summarized above) on 1,2,3-TCP genotoxic activity *in vivo* and *in vitro* are more extensively described and reviewed by IARC (1995) and WHO (2003).

Developmental and Reproductive Toxicity

Male and female CD rats were exposed to 1,2,3-TCP five days/week for 6 hours/day by inhalation at 0, 5 or 15 ppm for 10 weeks prior to mating and during the mating period (Johannsen *et al*., 1988). The female mice that were successfully mated were then exposed daily during the first 14 days of gestation. For females where no mating

occurred, exposure was continued while they were housed with other male(s) for additional 10 day periods until mating occurred. They were then exposed during the first 14 days of gestation. Additional mating periods were restricted to a maximum of four or forty days of exposure. In a follow up study, the mice were exposed to 0, 0.5 or 1.5 ppm 1,2,3-TCP due to low mating indices in the initial study.

In the initial study, the body weights of both sexes in the high-dose group (15 ppm) were lower than control, and body weight gain was significantly lower than control during the premating period. Body weight in the high-dose females also remained below that of the control group during the gestation and lactation period. Severe head tilt was observed in one low-dose female and six high-dose animals, which was suggested by the authors as being consistent with mycoplasma infection.

No difference was observed in mating performance and fertility index between the treated versus control groups in the initial or followup study. There were no differences between litter size, gestation length, mean pup body weight and number of surviving pups in the treated and control groups in the initial and followup study. No histopathology was observed in the testes, epididymes or ovaries in the treated animals.

1,2,3-TCP was evaluated for reproductive and developmental toxicology using a continuous breeding protocol in which toxicant exposure of males and females continues as animals breed, producing up to five litters per breeding pair (Chapin *et al.*, 1997; Gulati *et al*., 1991; WHO, 2003). Beginning seven days prior to breeding, 30, 60 or 120 mg/kg was administered by gavage in corn oil daily to male and female CD-1 mice for 14 weeks (Task 2). Fewer breeding pairs delivered litters by the third, fourth and fifth litters than in control animals. In the fifth litter, 87, 78, 68 and 42 percent of the pairs exposed to 0, 30, 60, and 120 mg/kg-day, respectively, delivered a litter. The decrease was statistically significant (42 percent) compared to control (87 percent) in the fifth litters of the high dose group. Overall (aggregating the results across all five litters), there was a 16 percent decrease in litters per breeding pair exposed to the high dose of 1,2,3-TCP and there were 47 percent fewer pups per litter.

Pups in the final litters (litter five) were reared by the dam, weaned and then exposed to TCP through mating (Task 4). Neither pup weights nor viability were noticeably affected following the exposure of the F_1 generation to 1,2,3-TCP. Because of the reduced number of litters in the high dose in Task 2, only nine breeding pairs were available in Task 4. Only three of nine breeding pairs in the high-dose group delivered a litter with any pups.

A crossover study in which high-dose females or males were bred with an untreated partner (Task 3) revealed fewer live pups when females were exposed and no noticeable reproductive toxicity when only males were exposed to 1,2,3-TCP. After the crossover breeding study, the adults were sacrificed. Increased liver and kidney weight was observed in the high-dose males, and increased liver weight was observed in the high-dose females. Four of ten females had microscopic ovarian amyloidosis compared to zero females in the control group.

Five doses of 80 mg/kg 1,2,3-TCP were administered to male rats by gavage (Saito-Suzuki *et al*., 1982). Following treatment, each rat was mated with an untreated female rat once a week for eight successive weeks. No significant changes from control levels

were observed for the following toxic endpoints: number of females with implants, numbers of corpora lutea per female, number of implants per female, numbers of live embryos per female, and mean number of dead implants.

Immunotoxicity

No data were located.

Neurotoxicity

Indication of CNS excitability was evaluated in mice treated with pentylenetetrazol (PTZ) which induces clonic convulsions in mice (Albrecht, 1987). Administration of 1,2,3-TCP by intraperitoneal injection (1.31×10^{-4} mol/kg) had no apparent effect on the ability of PTZ to induce convulsions.

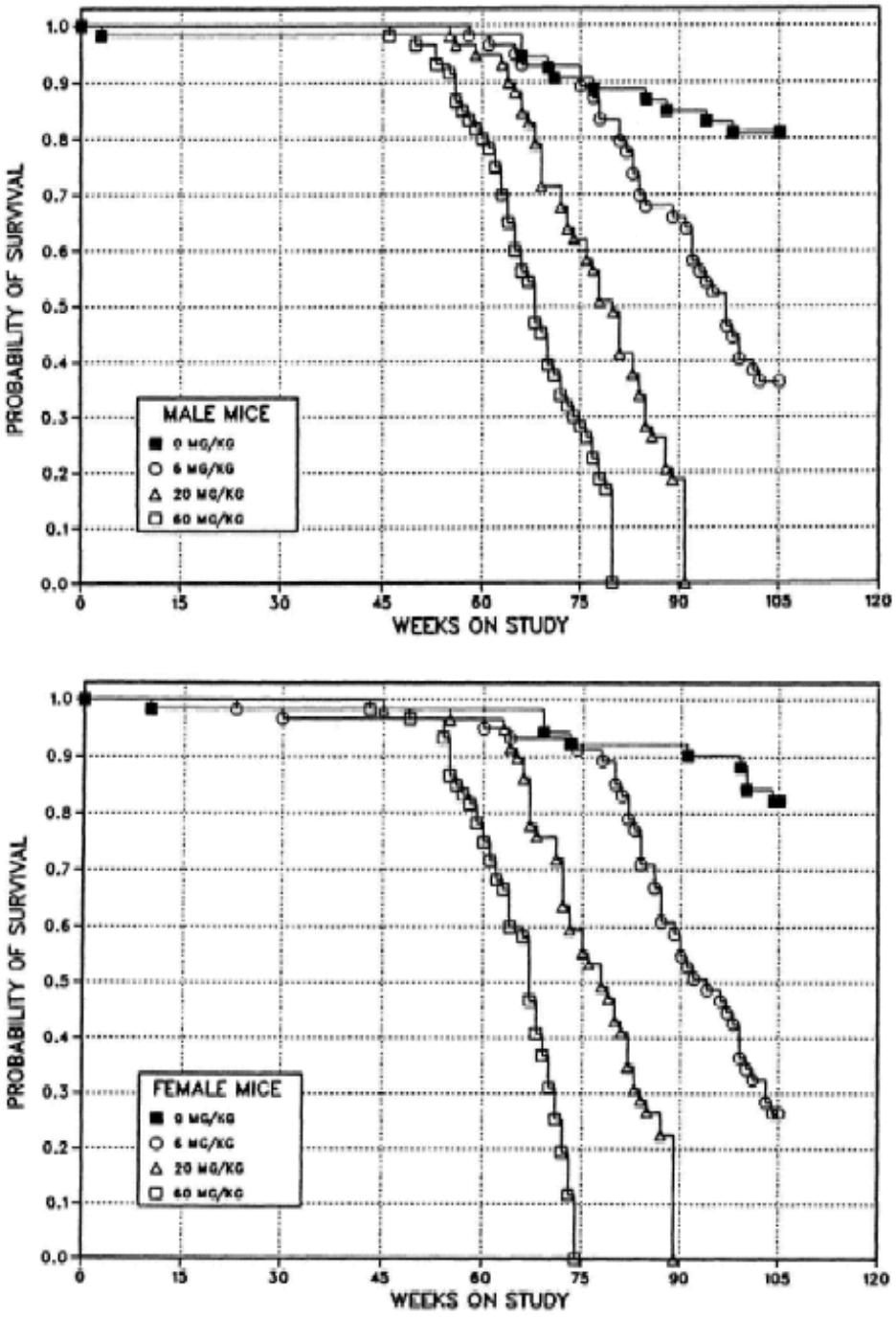
Chronic Toxicity/Carcinogenicity

Groups of 60 male or female rats (F-344) and mice ($B6C3F_1$) were administered 1,2,3-TCP by gavage in corn oil in a two-year cancer bioassay (NTP, 1993). Rats were administered 0, 5, 10 or 30 mg/kg-day of 1,2,3-TCP, 5 days/week while mice were administered 0, 10, 30 or 60 mg/kg-day, 5 days/week. The doses employed in this study were based on findings in a 17-week study in which higher doses of 1,2,3-TCP in rats and mice resulted in significant toxicity. It was reported that "up to 10" animals in each group were used for an interim sacrifice at 15 months.

The survival of mice was substantially reduced in the two highest dose groups administered 1,2,3-TCP (Figure 2). In mice, early deaths in the 60 mg/kg-day group were reported to result from chemically-related neoplasms, primarily forestomach tumors (NTP, 1993). Of the surviving mice in the 60 mg/kg-day group, the remaining males were sacrificed in week 79 and females in week 73 because of high mortality. Survival in the 20 mg/kg-day group was also reduced due to chemically-related tumors. Remaining mice in these dose groups were sacrificed in week 89 because of high mortality. The early death of mice in the two highest dose groups likely affected the incidence of tumors that would have been detected at certain sites (absent the early mortality), particularly tumors that were late developing.

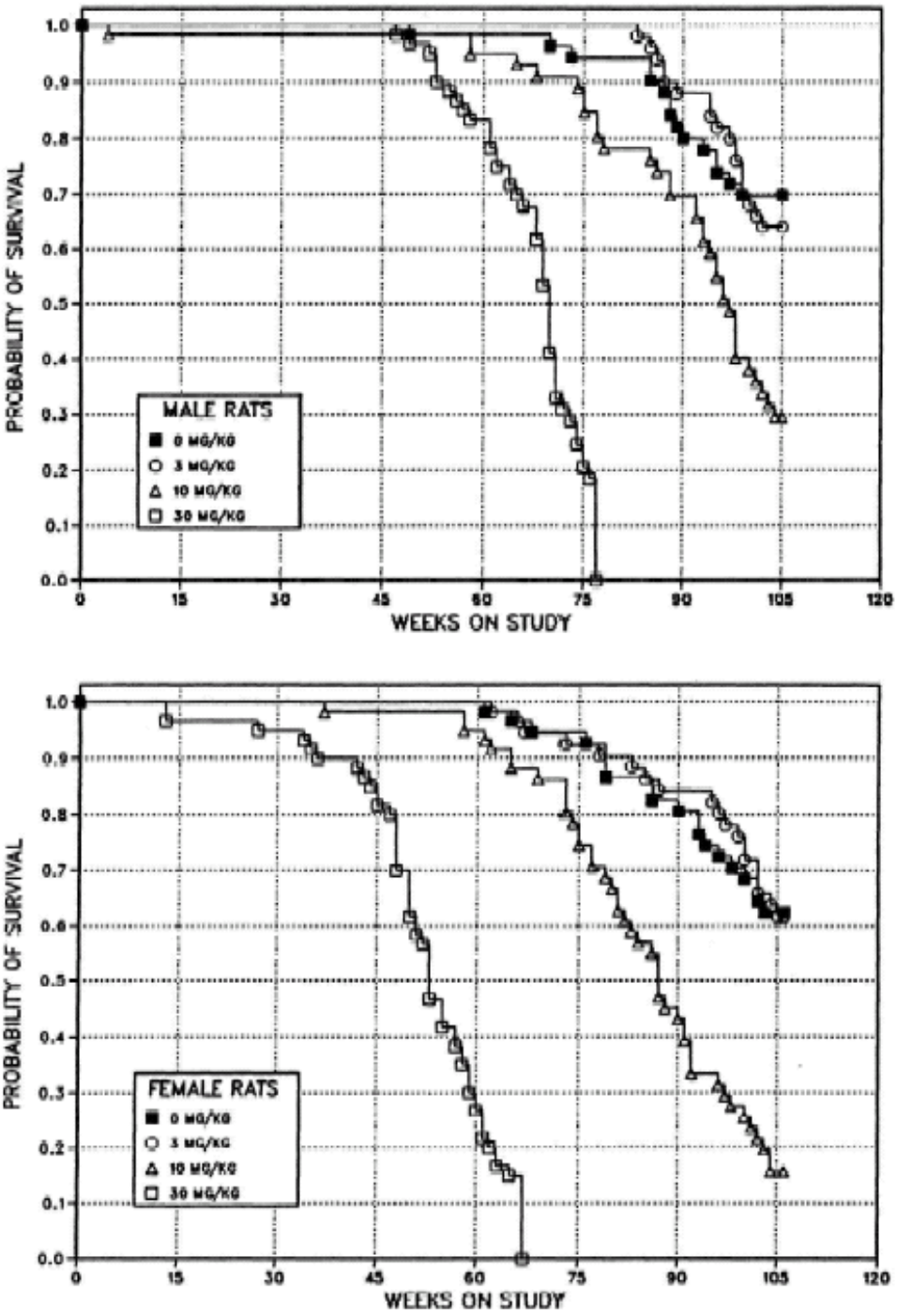
Analogous to what was observed in mice, the survival of rats in the two highest dose groups was markedly reduced (Figure 3). Early deaths were attributed to the occurrence of chemically-related neoplasms, but the site(s) were not specified. In the 30 mg/kg-day dose group, surviving female rats were sacrificed at week 66 and males at week 76 because of high mortality.

Figure 2. Survival of mice administered various doses of 1,2,3-trichloropropane[1]



[1]From NTP (1993)

Figure 3. Survival of rats administered various doses of 1,2,3-trichloropropane[1]



[1]From NTP (1993)

The administration of 1,2,3-TCP resulted in statistically significant increases in tumors at a number of sites in both male and female mice and rats (Tables 4 and 5). Results from the 15 month interim sacrifice groups are shown in Tables 6 and 7. In the male mouse, statistically significant or notable increases in neoplasms were observed in the forestomach, liver and Harderian gland. Statistically significant or notable increases in tumors were observed in the oral cavity, forestomach, liver, Harderian gland and uterus of female mice.

Table 4. Summary of Treatment-Related Tumors in the 2-Year 1,2,3-Trichloropropane Bioassay in B6C3F$_1$ Mice[1]

Male Mice	Female Mice
Forestomach: squamous cell papilloma (3/52, 28/51, 22/54, 33/56)[2] squamous cell carcinoma (0/52, 40/51, 50/54, 51/56) papilloma or carcinoma (3/52, 50/51, 53/54, 55/56)	Forestomach: squamous cell papilloma (0/50, 23/50, 18/51, 29/55) squamous cell carcinoma (0/50, 46/50, 49/51, 49/55) papilloma or carcinoma (0/50, 48/50, 50/51, 54/55)
Liver: hepatocellular adenoma (11/52, 18/51, 21/54, 29/56) hepatocellular carcinoma (4/52, 11/51, 5/54, 3/56) adenoma or carcinoma (13/52, 24/51, 24/54, 31/56)	Liver: hepatocellular adenoma (6/50, 9/50, 8/51, 31/55) hepatocellular carcinoma (1/50, 3/50, 0/51, 2/55) adenoma or carcinoma (7/50, 11/50, 8/51, 31/55)
Harderian gland: adenoma (1/52, 2/51, 10/54, 11/56)	Oral cavity: squamous cell carcinoma (0/50, 0/50, 1/51, 5/55)
	Uterus: adenoma (0/50, 1/50, 0/51, 3/54) adenocarcinoma (0/50, 4/50, 3/51, 6/54) adenoma or carcinoma (0/50, 5/50, 3/51, 9/54)

[1]Adapted from summary table in NTP, 1993.
[2]Number of tumor-bearing mice/number of mice necropsied in each dose group. Does not include animals in 15 month interim sacrifice group.

In the male rat, statistically significant or notable increases in neoplasms were observed in the oral cavity (tongue and pharynx), forestomach, pancreas, kidney, preputial gland and Zymbal gland. Statistically significant or notable increases in tumors were observed

in the oral cavity, forestomach, clitoral gland, mammary gland and Zymbal gland of female rat.

Table 5. Summary of Treatment-Related Tumors in the 2-Year 1,2,3-Trichloropropane Cancer Bioassay in the F-344 Rat[1]

Male Rats	Female Rats
Oral cavity: squamous cell papilloma (0/50, 4/50, 9/49, 19/52)[2] squamous cell carcinoma (1/50, 0/50, 11/49, 25/52) papilloma or carcinoma (1/50, 4/50, 18/49, 40/52) [2]	Oral cavity: squamous cell papilloma (1/50, 5/49, 10/52, 18/52) squamous cell carcinoma (0/50, 1/49, 21/52, 21/52) papilloma or carcinoma (1/50, 6/49, 28/52, 32/52)
Forestomach: squamous cell papilloma (0/50, 29/50, 33/49, 38/52) squamous cell carcinoma (0/50, 9/50, 27/49, 13/52) papilloma or carcinoma (0/50, 33/50, 42/49, 43/52)	Forestomach: squamous cell papilloma (0/50, 13/49, 32/51, 17/52) squamous cell carcinoma (0/50, 3/49, 9/51, 4/52) papilloma or carcinoma (0/50, 16/49, 37/51, 19/52)
Pancreas: acinar adenoma (5/50, 21/50, 36/49, 29/52) adenocarcinomas (0/59, 0/50, 2/49, 1/52) papilloma or adenocarcinoma (5/50, 21/50, 36/49, 29/52)	Clitoral gland: adenoma (5/46, 10/46, 13/50, 10/51) carcinoma (0/46, 0/46, 4/50,6/51) papilloma or carcinoma (5/46, 10/46, 17/50, 15/51)
Kidney: renal tubule adenoma (0/50, 2/50, 20/49, 21/52)	Mammary gland: adenoma (1/50, 0/40, 3/52, 0/52) adenocarcinoma (1/50, 6/49, 12/52, 21/52)
Preputial gland: adenoma (5/49, 3/47, 5/49, 11/50) carcinoma (0/49, 3/47, 3/49, 5/50) papilloma or carcinoma (5/49, 6/47, 8/49, 16/50)	Zymbal's gland: carcinoma (0/50, 1/49, 0/52, 3/52)
Zymbal's gland: carcinoma (0/50, 0/50, 0/49, 3/52)	

[1]Adapted from summary table in NTP, 1993).
[2]Number of tumor bearing rats/number of rats necropsied in each dose group. Does not include animals in 15 month interim sacrifice group.

Table 6. Summary of Treatment-Related Tumors in the 15 month Interim Sacrifice Group of the 1,2,3-Trichloropropane Cancer Bioassay in the B6C3F$_1$ Mice[1]

Male Mice	Female Mice
Forestomach: squamous cell papilloma (0/8, 7/8, 3/6, 2/4)[2] squamous cell carcinoma (0/8, 1/8, 4/6, 4/4) papilloma or carcinoma (0/8, 7/8, 4/6, 4/4)	Forestomach: squamous cell papilloma (0/10, 5/10, 9/9, 4/5) squamous cell carcinoma (0/10, 1/10, 6/9, 2/5) papilloma or carcinoma (0/10, 6/10, 9/9, 5/5)
Liver: hepatocellular adenoma (1/8, 0/8, 0/6, 2/4) hepatocellular carcinoma (0/8, 0/8, 1/6, 0/4) adenoma or carcinoma (1/8, 0/8, 1/6, 2/4)	Liver: hepatocellular adenoma (1/10, 0/10, 1/9, 5/5) hepatocellular carcinoma (0/10, 0/10, 0/9, 0/5) adenoma or carcinoma (1/10, 0/10, 1/9, 5/5)
Harderian gland: adenoma (0/8, 0/8, 0/6, 0/4)	Oral cavity: squamous cell carcinoma (0/10, 0/10, 0/9, 0/5)
	Uterus: adenoma (0/10, 0/10, 0/9, 1/5) adenocarcinoma (0/10,0/10, 0/9, 2/5) adenoma or carcinoma (0/10, 0/10, 0/9, 3/5)

[1]Adapted from summary table in NTP, 1993.
[2]Number of tumor-bearing mice/number of mice necropsied in each dose group.

Table 7. Summary of Treatment-Related Tumors in the 15 month Interim Sacrifice Group of the 1,2,3-Trichloropropane Cancer Bioassay in the F-344 Rat[1]

Male Rats	Female Rats
Oral cavity: squamous cell papilloma (0/10, 0/10, 1/10, 3/8)[2] squamous cell carcinoma (0/10, 0/10, 0/10, 0/8)[2] papilloma or carcinoma (0/10, 0,10, 1.10, 3/8)[2]	Oral cavity: squamous cell papilloma (0/10, 0/10, 0/8, 3/8) squamous cell carcinoma (0/10, 0/10, 0/8, 2/8) papilloma or carcinoma (0/10, 0/10, 0/8, 5/8)
Forestomach: squamous cell papilloma (0/10, 2/10, 3/10, 8/8) squamous cell carcinoma (0/10, 0/10, 1/10, 1/8) papilloma or carcinoma (0/10, 2/10, 4/10, 8/8)	Forestomach: squamous cell papilloma (0/10, 1/10, 5/8, 7/8) squamous cell carcinoma (0/10, 0/10, 0/10, 2/8) papilloma or carcinoma (0/10, 1/10, 5/8, 8/8)
Pancreas: acinar adenoma (0/10, 0/10, 1/10, 2/8) adenocarcinomas (0/10, 0/10, 0/10, 0/8) papilloma or adenocarcinoma (0/10, 0/10, 1/10, 2/8)	Clitoral gland: adenoma (0/10, 1/10, 1/8, 2/8) carcinoma (0/10, 0/10, 0/8, 0/8) papilloma or carcinoma (0/10, 1/10, 1/8, 2/8)
Kidney: renal tubule adenoma (0/10, 0/10, 0/10, 5/8)	Mammary gland: adenoma (0/10, 0/10, 0/8, 1/8) adenocarcinoma (0/10, 0/10, 0/8, 1/8)
Preputial gland: adenoma (0/10, 0/10, 1/10, 0/8) carcinoma (0/10, 0/10, 0/10, 1/8) papilloma or carcinoma (0/10, 0/10, 1/10, 1/8)	Zymbal's gland: carcinoma (0/10, 0/10, 0.8, 1/8)
Zymbal's gland: carcinoma (0/10, 0/10, 0/10, 0/8)	

[1]Adapted from summary table in NTP, 1993.
[2]Number of tumor bearing rats/number of rats necropsied in each dose group.

No significant adverse effects unrelated to the occurrence of neoplasms were reported in animals in the 2-year study. NTP reported for the rat: "Of the clinical findings, none were considered to be directly related to organ toxicity other than those associated with chemical-induced neoplasms of the oral mucosa, forestomach or mammary glands." For

mice NTP reported “no clinical findings were considered to be directly related to organ toxicity other than those associated with chemical-induced neoplasms.”

Toxicological Effects in Humans

Acute Toxicity

Acute exposure to 1,2,3-TCP resulted in eye and throat irritation (reviewed by ATSDR, 1992; WHO, 2003). Acute CNS effects have also been reported (HSDB, 2005).

Subchronic Toxicity

No data were located.

Neurotoxicity

No data were located.

Immunotoxicity

No data were located.

Developmental/Reproductive Toxicity

No data were located.

Chronic Toxicity

No data were located.

1,2-Dibromo-3-chloropropane (DBCP)

DBCP, which is a halogenated propane that is closely-related structurally to 1,2,3-TCP, also tested positive for carcinogenic activity in rats and mice when administered by gavage in corn oil (NCI, 1978) or by inhalation (NTP, 1982). Statistically significant increases in carcinomas of the forestomach were observed in male and female rats and mice in the oral study. In the inhalation study, increases in carcinomas of the nasal cavity and papillomas of the tongue were observed in both sexes in the rat (NTP, 2004). In male and female mice, inhalation exposure resulted in carcinomas of the nasal cavity and alveolar/bronchial adenomas or carcinomas of the lung (NTP, 2004).

Metabolism of DBCP and 1,2,3-TCP appears to be similar, involving cytochrome P450s and also a glutathione pathway. The same major DNA adduct, S-[1-(hydroxymethyl)-2-(N7-guanyl)ethyl]glutathione has been detected in rats and mice following DBCP or 1,2,3-TCP administration (IARC, 1999).

Evidence for Carcinogenic Activity of 1,2,3-Trichloropropane

Animal Studies

The administration of 1,2,3-TCP in corn oil by gavage to rats and mice resulted in a statistically significant increase in tumors in multiple organs in both male and female mice and rats. Tumors occurred in tissues that were in direct contact with the administered compound (oral cavity, forestomach) and also in tissues distal to the site of administration (liver, Harderian gland, uterus). The increase in tumors also appeared to be dose-dependent (see Tables 4 and 5 and also NTP (1993) Tables 7, 8, 11, 20, 21, 22, 23).

Human Studies

No studies were identified that evaluated carcinogenic effects of 1,2,3-TCP in humans.

Genotoxicity

1,2,3-TCP was generally positive in both *in vivo* and *in vitro* genotoxicity studies. The compound was positive in *in vitro* assays in the presence of metabolic activation and negative without metabolic activation. *In vivo* studies revealed single strand chromosome breaks in rat liver and kidney. Studies also revealed the formation of DNA adducts following the administration of 1,2,3-TCP to rats or mice.

Mechanism

Studies have indicated cytochrome P450 has a role in metabolizing 1,2,3-TCP to an active form. Activation may also involve reaction with glutathione. Glutathione conjugation also appears to inactivate the toxicant. Genotoxicity studies have demonstrated the formation of DNA adducts following the administration of TCP. Agents that alter TCP metabolism by inducing cytochrome P450 or inhibiting metabolism by cytochrome P-450 or agents that deplete glutathione in the cell altered the amount of 1,2,3-TCP metabolite that bound to protein or DNA.

Conclusion

1,2,3-TCP was a potent carcinogen by gavage in the available cancer bioassays conducted in rats and mice. 1,2,3-TCP also tested positive in a number of *in vivo* and *in vitro* genotoxicity studies. Therefore it is prudent to assume that 1,2,3-TCP represents a significant carcinogenic risk when it occurs in drinking water.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

1,2,3-Trichloropropane was administered in corn oil by gavage to rats and mice five days a week for up to 17 weeks in a study aimed at identifying doses for a two-year cancer bioassay (NTP, 1993). Rats appeared to be more sensitive than mice to the adverse effects. Effects on the liver (increased absolute and relative liver weight) were observed at doses as low as 32 mg/kg-day (males) and 16 mg/kg-day (females). Histopathology in the liver was observed at 125 or 250 mg/kg. Effects on absolute and relative kidney weights were observed in males treated with 32 mg/kg-day and females receiving 63 mg/kg-day. Regenerative hyperplasia was observed in the kidney of male and female rats receiving doses as low as 64 mg/kg-day after eight weeks of treatment.

Total bilirubin values were increased at 63 and 125 mg/day in male and female rats. Increases in serum enzymes associated with liver toxicity were observed at dose as low as 63 to 125 mg/kg-day. Effects on erythrocytes (decreased erythrocyte mass, lower mean hematocrit, hemoglobin and erythrocyte counts) were observed in male and female rats at doses as low as 16 mg/kg-day. No toxic effects that were not related to the occurrence of tumors were identified in the subsequent two-year cancer bioassay.

Reproductive /developmental effects associated with exposure to 1,2,3-TCP occurred at much higher levels of exposure than effects that were observed in the aforementioned 17 week study. Therefore, based on effects on erythrocytes at 16 mg/kg-day, 8 mg/kg-day (administered dose) is identified as the no observed adverse effects level (NOAEL). This dose, administered 5 days/week, is corrected to a 7 days/week equivalent as follows:

8 mg/kg * (5 days/week / 7 days/week) = 5.7 mg/kg-day

Carcinogenic Effects

The administration of 1,2,3-TCP to male or female rats and mice resulted in statistically significant increases in tumors at a number of sites (NTP, 1993). At some sites (forestomach and clitoral gland in female rats), incidence of tumors at the high dose was less than at the middle dose. This may have been due to shorter survival of the animals, which may have prevented the occurrence or detection of tumors at the site (although shortened survival would not alter the incidence of a tumor at the site that caused the death, or for tumors that were detected prior to or at death). The incidence of late occurring tumors would be expected to be influenced by changes in survival. At some sites (e.g., the forestomach), tumors occurred in nearly 100 percent of the animals that received 1,2,3-TCP. This finding complicates dose-response calculations. However, the tumors tended to occur earlier in animals that received higher doses.

Both the notable shortening of lifespan and its probable effect on incidence of tumors at many of the sites, and the high incidence of tumors in a number of dose groups suggest that at certain sites, a time-to-tumor model is most appropriate to estimate 1,2,3-TCP cancer potency. The time-to-tumor model takes into consideration both how many tumors occurred and when they occurred. Reporting in the NTP (1993) study of when

and what types of tumors were observed in each animal allows for a time-to-tumor analysis. Unfortunately the cause of death of individual animals was not reported.

A time-to-tumor model that is multistage in dose and Weibull in time (Tox_Risk v. 5.2) was employed to develop a dose-response relationship for various tumor sites in male and female rats and mice (Crump *et al*., 2000). The dose in animals was adjusted to reflect daily exposure to 1,2,3-TCP (multiplied by 5/7) and scaled to humans based on the ratio of human and animal body weights to the ¾ power. The model default body weights of 350 g for rats and 30 g for mice were used. While a number of tumor sites could have been selected, the modeling focused on sites with a high incidence of tumors.

NTP reported that mortality was related to the occurrence of tumors. However, because tumors occurred at multiple sites in many of the animals, it is unclear which tumor was the cause of death in a given animal (although the NTP did report that early deaths in mice from the high dose groups (60 mg/kg-day) were due to chemical-related neoplasms, primarily in the forestomach (NTP, 1993). In a separate publication, the investigators reported: "Neoplasms of the forestomach in rats and mice, of the oral mucosa in rats and mammary gland in female rats, were the principal cause of death of most animals dying or killed moribund before the end of the study" (Irwin *et al*., 1995).

Given the multiplicity of tumor sites, an analysis based on the assumption that tumors at each of the sites were responsible for the animal's death appeared to be inappropriate except perhaps for forestomach tumors in mice, based on the NTP (1993) comment that early deaths in mice from the high dose groups (60 mg/kg-day) were due to chemical-related neoplasms, primarily in the forestomach. Assuming that all tumors were incidental at the time of death (not the cause of it) also appears to be inappropriate given the animals were reported to be dying from chemically-related tumors. Because the causes of deaths for individual animals were not provided, a middle position was employed in the assignment of data for the time-to-tumor modeling, where carcinomas were judged to be fatal and papillomas and adenomas were assumed to be incidental to the cause of death for the modeling. This would be a better approximation of the potential causes of death than either of the extremes, and the model requires assignment of cause of death. Animals exhibiting both adenomas and carcinomas at a site were evaluated based on the occurrence of the carcinoma.

Separate analyses of the findings in mice were performed for tumors of the forestomach: 1.) where all forestomach tumors were considered to be incidental to the cause of death of the animal, and 2.) where forestomach tumors were presumed to be the cause of death of the animal. These separate analyses were undertaken to determine the impact of the assumption regarding the cause of death on the dose response relationship based on a time-to-tumor model.

NTP did not report the findings of individual animals in the 15 month interim sacrifice groups in its technical report but did provide the specific findings on its internet site (NTP, 2007). We performed a separate analysis that included the results from animals in the interval (66 weeks) sacrifice groups. For this analysis, the occurrence of tumors in the interim sacrifice groups was judged to be incidental to the cause of death of the animals.

The results of the time-to-tumor analysis with different assumption about cause of death are shown in Table 8. A lower-bound estimate (the 95th percent lower confidence limit) of the dose associated with a 10 percent tumor incidence (LED_{10}) is based on lifetime (70 years) exposure.

Table 8. 1,2,3-Trichloropropane Potency Estimates using a Time-to-Tumor Model

Species	Sex	Tumor Site	Human q_1* $(mg/kg\text{-}day)^{-1}$	LED_{10} (μg/kg-day)
Rat	Male	Forestomach[1]	3.0	36
	Female	Forestomach[1]	0.9	110
	Male	Oral Cavity[1]	0.2	460
	Female	Oral Cavity[1]	0.3	350
	Male	Preputial[1]	0.2	590
	Female	Mammary[1]	1.0	110
	Male	Pancreas	1.4	77
Mouse	Male	Forestomach[1]	16	6.8
	Female	Forestomach[1]	17	6.1
	Male	Forestomach[1,2]	19	5.5
	Female	**Forestomach[1,2,3]**	**26**	**4.0**
	Male	Forestomach[4]	22	4.8
	Female	Forestomach[4]	1900	0.07
	Male	Forestomach[2,4]	22	4.8
	Female	Forestomach[2,4]	180	0.6
	Male	Forestomach[5]	4.4	23.7
	Female	Forestomach[5]	11	9.4
	Male	Liver[1]	1.8	59
	Female	Liver[1]	0.9	110

[1]Where carcinomas are considered to be fatal tumors and adenomas are considered to be incidental (not the cause of death in the animal).
[2]Includes interim sacrifice groups.
[3]Used to derive the cancer slope factor (CSF) for 1,2,3-TCP.
[4]Where carcinomas and papillomas were considered to be incidental (incidental to the cause of death in the animal).
[5]Where carcinomas and papillomas were considered to be fatal (the cause of death in the animal).

The assumption that all tumors were incidental to the cause of death of the animals had a marked effect on the cancer potency estimate, q_1*, while the assumption that all tumors were the cause of death in the animals had little effect on q_1*. Including the interim

sacrifice groups in the modeling had little effect on the q_1* except when all tumors were assumed to be incidental to the cause of death of the animal.

The middle position, where carcinomas were judged to be fatal while papillomas and adenomas were assumed to be incidental to the cause of death, was selected as the basis for developing a dose-response relationship for the PHG. This is judged to be the most reasonable and likely the most accurate approximation of the distribution of the outcomes. With this strategy, the female mouse forestomach yielded the highest estimate of potency q_1*, 26 $(mg/kg\text{-}day)^{-1}$ and the lowest estimate of the lower 95th percent confidence interval of the dose associated with a 10 percent tumor incidence (LED_{10}), 4.0 μg/kg-day. The linear slope associated with the dose response relationship is calculated from the LED_{10} dose and the response of $1/10^{th}$ of the animals for forestomach tumors in the female mouse as:

$$\frac{0.1}{LED_{10}} = \frac{0.1}{0.004 \text{ mg/kg-day}} = 25 \text{ mg/kg-day}^{-1}$$

For comparative purposes, dose responses for tumors at each site were also determined using a linearized multistage (LMS) model, although the goodness of fit for tumors in the forestomach in rats and mice was very poor using all dose groups ($p < 10^{-6}$). The high dose groups were eliminated and the model was run until a goodness of fit of > 0.1 was achieved.

As expected, the time to tumor model yielded higher estimates of potency than the LMS model because it accounted for the early deaths in the animals that prevented the observation of late occurring tumors. The lower-bound estimate (the lower 95^{th} percent confidence limit) of the dose associated with 10 percent incidence of tumors (LED_{10}) in the forestomach in the male rat using a Linearized Multistage Model is 0.058 mg/kg-day. Using a linear model, the slope of the dose-response relationship associated with forestomach tumors in male rats (the highest rat potency) is 0.1 / 0.058 mg/kg-day = 1.7 $(mg/kg\text{-}day)^{-1}$. The LED_{10} for forestomach tumors in the female mouse using a Linearized Multistage Model is 0.015 mg/kg-day. Using a linear model, the slope of the dose-response relationship associated with forestomach tumors in female mice is 0.1 / 0.015 mg/kg-day = 6.7 $(mg/kg\text{-}day)^{-1}$.

CALCULATION OF PHG

Noncarcinogenic Effects

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose (ADD) of the chemical from all sources will first be calculated. This involves incorporation of appropriate estimates of uncertainty in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime daily

dose for that is unlikely to result in any toxic effects. For this purpose, the following equation will be used:

$$\text{ADD} = \frac{\text{NOAEL/LOAEL in mg/kg-day}}{\text{UF}}$$

where,

ADD = acceptable daily dose, an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects;

NOAEL/LOAEL = no-observed-adverse-effect level or lowest-observed-adverse-effect level in the critical study;

UF = uncertainty factor.

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for noncarcinogenic endpoints:

$$\text{C} = \frac{\text{ADD mg/kg-day x BW kg/day x RSC}}{\text{L/day}}$$

where,

BW = body weight (a default of 70 kg for adult males, 60 kg for adult females, or 25 kg for a child);

RSC = relative source contribution, usually 20 to 80 percent (0.20 to 0.80);

L/day = volume of water consumed daily for an adult or child (defaults of 2 L/day and 1 L/day, respectively, which may be corrected for exposures to the chemical from other household uses of tap water).

The most robust data available for calculation of the health protective level based on noncarcinogenic effects were from a 17-week subchronic study conducted in F-344 rats (NTP, 1993). A NOAEL of 8 mg/kg-day was identified based on effects on erythrocytes at the next higher dose, 16 mg/kg-day. A dose of 8 mg/kg administered 5 days/week corresponds to 5.7 mg/kg-day when adjusted to reflect daily dosing. Use of an uncertainty factor of 1,000 was considered appropriate to account for the use of subchronic toxicity data (10), for interspecies differences (10), and for human variability (10). Thus, the ADD is calculated as:

$$\text{ADD} = \frac{\text{5.7 mg/kg-day}}{\text{1,000}} = \text{5.7 μg/kg-day}$$

Based on data for water consumption by the general population in the Western Region of the U.S. (OEHHA, 2000), water ingestion of 2.0 L/day was assumed. Contributions from inhalation and dermal exposure to 1,2,3-TCP in tap water in the home were estimated as 2 L_{eq}/day and 0 L_{eq}/day, respectively (see Exposure section). Adding up exposure by the different routes leads to a total drinking water consumption of 4 L_{eq}/day for 1,2,3-TCP.

Using the adjusted NOAEL value, 70 kg body weight, 80 percent relative source contribution (no other substantive sources of environmental exposure were identified), and a combined 4 L_{eq}/day drinking water consumption rate, the public health protective concentration for noncarcinogenic effects is calculated as follows:

$$C = \frac{5.7\ \mu g/kg\text{-}day \times 70\ kg \times 0.80}{4.0\ L_{eq}/day} = 0.08\ mg/L = 80\ ppb$$

The health-protective concentration for 1,2,3-TCP based on a noncancer endpoint for the general population is therefore 0.08 mg/L or 80 ppb.

Carcinogenic Effects

For carcinogens, the following general equation can be used to calculate the public health-protective concentration (C) of a chemical in drinking water (in mg/L):

$$C = \frac{R \times BW}{CSF \times WC} = mg/L\ (ppm)$$

where,

R = *de minimis* lifetime excess individual cancer risk (a default of 10^{-6});

BW = adult body weight (a default of 70 kg);

CSF = cancer slope factor (upper bound estimate), cancer potency derived from the lower 95 percent confidence limit on the dose associated with a 10 percent tumor incidence (LED_{10});

WC = volume of water consumed daily (L/d), which may include a multiroute exposure estimate for volatile organic compounds (i.e., L_{eq}/d).

The most sensitive cancer endpoint for 1,2,3-TCP was an increase in tumors in the forestomach of the female mouse (NTP, 1993). The concentration of 1,2,3-TCP in water equivalent to a lifetime risk of 10^{-6} was calculated using a time-to-tumor model to estimate the low bound of the dose associated with a risk of 10^{-1}. A linear dose response model was then employed to obtain an oral slope factor of 25 $(mg/kg\text{-}day)^{-1}$. The health protective concentration was calculated using oral data only, as no data on the carcinogenicity of 1,2,3-TCP via the inhalation route were available.

The default adult body weight of 70 kg was used in the calculation. Based on data for water consumption by the general population in the Western Region of the U.S. (OEHHA, 2000), a water ingestion amount of 2.0 L/day was assumed. The contributions from inhalation and dermal exposure to 1,2,3-TCP in tap water in the home were 2 L_{eq}/day and 0 L_{eq}/day, respectively (see Exposure section). Adding up exposure by the different routes leads to a total drinking water consumption of 4 L_{eq}/day for 1,2,3-TCP.

Using the cancer slope factor (upper bound estimate) of 25 $(mg/kg\text{-}day)^{-1}$, the estimated health-protective value is therefore:

$$C = \frac{10^{-6} \times 70\ kg}{25\ (mg/kg\text{-}day)^{-1} \times 4\ L_{eq}/day} = 0.0007\ \mu g/L = 0.0007\ ppb$$

Calculating the health-protective value for 1,2,3-TCP using a linear cancer extrapolation model and a *de minimis* 10^{-6} lifetime theoretical cancer risk results in a PHG of 0.0007 µg/L or 0.0007 ppb. The corresponding values at 10^{-5} and 10^{-4} risk are 0.007 and 0.07 µg/L (ppb), respectively. The PHG based on cancer effects would also be protective against noncancer effects.

RISK CHARACTERIZATION

The PHG for 1,2,3-TCP of 0.0007 ppb is based on risk associated with ingestion of drinking water and inhalation of 1,2,3-TCP that volatilizes from the tap water during showering and other household water uses. Dermal exposures were estimated to be insignificant relative to direct ingestion and inhalation. Various sources of uncertainty regarding the development of health-protective criteria for the oral and inhalation routes are discussed.

Hazard Identification - There is considerable evidence that exposure to 1,2,3-TCP results in increased incidences of cancer in animals, based on the results of the 1993 NTP cancer bioassays. No other comparable cancer studies were identified. Marked increases in tumors were observed in both male and female rats and mice at multiple sites, and the increases appeared to be dose-related. 1,2,3-Trichloropropane was positive in genotoxicity assays and DNA adducts have been detected in rats and mice and identified following exposure to 1,2,3-TCP.

Dose Response – A time-to tumor model was employed to develop a dose-response relationship for various tumors in male and female rats and mice. 1,2,3-TCP was a potent tumorigenic agent at many sites. In both rats and mice, the animals died early and the deaths were judged to be due to the tumors. The early deaths would also affect the incidence of tumors at other sites. The time to tumor model used information regarding how many tumors occurred and when they occurred to develop a dose response relationship. The NTP (1993) study did not provide details on the cause of death of individual animals but did indicate that neoplasms of the forestomach were the principal cause of most of the early deaths. Given the uncertainty of the cause of death in a given animal, carcinomas were assumed to be lethal while adenomas and other benign tumors were considered to be incidental to the cause of death. Alternatively, the modeling could

have been based on all tumors being fatal and all tumors being incidental. Given the multiplicity of tumors in most animals, it is imprudent to assume that tumors at all sites caused the death of each animal, or, given the early mortality of the animals, that the tumors were incidental to the early death of the animals (especially since NTP concluded that the deaths were related to tumors).

Exposure Assessment – The default upper-bound estimate of drinking water ingestion (2 L/day) was employed to assess oral exposure to 1,2,3-TCP. The contribution of other exposure routes was estimated using the CalTOX model (DTSC, 1994). While exposure via the dermal route was determined to contribute a negligible portion of the overall dose, inhalation exposure was estimated to contribute approximately 50 percent of the daily dose (2 L_{eq}/day). The default adult body weight of 70 kg was used in the calculation. The non-cancer health-based criterion also reflects a relative source contribution of 80 percent of the total exposure coming from drinking water, because no other significant sources of exposure were identified. The RSC is not used in the cancer calculation because the cancer risk is calculated as "extra" risk, which would be in addition to other sources of exposure to the chemical.

Risk Characterization - The various sources of uncertainty attendant in the hazard identification, dose response, and exposure assessment are reflected in the estimates of a health-protective concentration of 1,2,3-TCP in drinking water. As better studies of the toxicity of 1,2,3-TCP, better methods to characterize the dose response relationship, and better methods to characterize exposure become available, the uncertainties associated with the risk assessment can be reduced. With the presently available information, the risk associated with exposure to 1,2,3-TCP may have been under- or overestimated. To address this uncertainty, the cancer risk assessment utilized an upper bound estimate of potency in the development of the health-based criterion, to ensure that risk is not markedly underestimated.

No sensitive populations were identified. OEHHA concludes that pregnant women and their fetuses, infants, the elderly, and other potentially sensitive populations will be adequately protected by this PHG.

OTHER REGULATORY STANDARDS

There are no State of California or federal MCLs for 1,2,3-TCP. U.S. EPA published an oral slope factor of 7 $(mg/kg\text{-}day)^{-1}$ in its HEAST summary table (U.S. EPA, 1997). DPH has developed a California Notification Level of 0.005 ppb based on the HEAST oral slope factor, which is also the detection limit for reporting (DHS, 2005).

The U.S. EPA developed an RfD of 0.006 mg/kg-day based on a non-cancer endpoint, alterations in clinical chemistry and reduction in red cell mass (U.S. EPA, 2007b; file section last updated 08/01/1990). The Permissible Exposure Limit (PEL) developed by the federal Occupational Safety and Health Administration (OSHA) for 1,2,3-TCP is 50 ppm or 300 mg/m^3. The concentration in air rated as an Immediate Danger to Life and Health (IDLH) is 100 ppm (NIOSH, 2004). The National Institute for Occupational

Safety and Health (NIOSH) recommended exposure limit (REL) for 1,2,3-TCP is 10 ppm and NIOSH considers 1,2,3-TCP as a potential occupational carcinogen (NIOSH, 2004).

The overall evaluation of the International Agency for Research on Cancer (IARC) is that 1,2,3-TCP is probably carcinogenic to humans (Group2A) (IARC, 1995). IARC concluded that there is inadequate evidence in humans and sufficient evidence of carcinogenicity in experimental animals. NTP concluded that 1,2,3-TCP is reasonably anticipated to be a human carcinogen based on sufficient evidence of malignant tumor formation at multiple sites in multiple species of experimental animals (NTP, 2004).

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