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Derivation of a reference dose and drinking water equivalent level for 1,2,3-trichloropropane

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ABSTRACT

In some US potable water supplies, 1,2,3-trichloropropane (TCP) has been present at ranges of non-detect to less than 100 ppb, resulting from past uses. In subchronic oral studies, TCP produced toxicity in kidneys, liver, and other tissues. TCP administered by corn oil gavage in chronic studies produced tumors at multiple sites in rats and mice; however, interpretation of these studies was impeded by substantial premature mortality. Drinking water equivalent levels (DWELs) were estimated for a lifetime of consumption by applying biologically-based safety/risk assessment approaches, including Monte Carlo techniques, and with consideration of kinetics and modes of action, to possibly replace default assumptions. Internationally recognized Frameworks for human relevance of animal data were employed to interpret the findings. Calculated were a reference dose (=39 μg/kg d) for non-cancer and Cancer Values (CV) (=10–14 μg/kg d) based on non-linear dose–response relationships for mutagenicity as a precursor of cancer. Lifetime Average Daily Intakes (LADI) are 3130 and 790–1120 μg/person-d for non-cancer and cancer, respectively. DWELs, estimated by applying a relative source contribution (RSC) of 50% to the LADIs, are 780 and 200–280 μg/L for non-cancer and cancer, respectively. These DWELs may inform establishment of formal/informal guidelines and standards to protect public health.

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1. Introduction

1,2,3-Trichloropropane (TCP), a chlorinated alkane, is manufactured for use as an intermediate in chemical processing, and has been used as a solvent, paint remover, and degreasing agent. It may also be produced as a by-product during the processing of other chlorinated compounds, such as epichlorohydrin (Bikales, 1969; WHO, 2003). Historically, TCP has been reported to have been present in certain soil fumigant pesticides (WHO, 2003). TCP is structurally similar to compounds of recognized toxicity such as 1,2-dibromo-3-chloropropane (DBCP).

Primary exposure of the general population to TCP appears to be via either water or air; however, it might be incorporated in foods that come into contact with TCP-containing irrigation water or tap water used in food preparation. Presently, while few data are available on environmental levels of TCP, concentrations ranging from 0.1 to 74 μg/L (ppb) have been detected historically in drinking water in Hawaii and California (ATSDR, 1992; WHO, 2003; HSDB, 2009; CDPH, 2007). In Hawaii, however, the levels in finished drinking water have been below the State standard (0.6 ppb) for many years, since all groundwater containing TCP is treated with granular activated carbon to remove this compound (Kawata, 1992). ATSDR (1992) reported from the US Environmental Protection Agency (US EPA) STORET database that in the mid-1980s

Abbreviations: AA, acrylamide; AIC, Akaike's Information Criterion; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ATSDR, Agency for Toxic Substances and Disease Registry; BMD, benchmark dose; BMD10, benchmark dose corresponding to a 10% increase in extra risk; BMDL, benchmark dose lower bound (corresponding to 95% lower confidence limit); BMDS, benchmark dose software; bw, body weight; BUN, blood urea nitrogen; CHO, Chinese hamster ovary; CI, confidence interval; CV, cancer value (RfD-equivalent); DBCP, 1,2-dibromo-3-chloropropane; DCA, 1,3-dichloroacetone; DHS, Department of Health Services; DWEL, drinking water equivalent level; EMS, ethylmethane sulfonate; ENU, ethylnitrosoura; GA, glycidamide; IPCS, International Programme on Chemical Safety; LADI, Lifetime Average Daily Intake; LB, lower bound from 90th percentile confidence interval; LI, BrdU Labeling Index; LOAEL, lowest-observed adverse effect level; MCL, Maximum Contaminant Level; MCLG, Maximum Contaminant Level Goal; MMS, methylmethane sulfonate; MNU, methylnitrosourea; MTD, maximum tolerated dose; MN, micronucleus; MoA, mode of action; N^7-GA-Gua, glycidamide (GA)-derived DNA adduct, N^7-(2-carbomyl-2-hydroxyethyl)guanine; NOAEL, no-observed adverse effect level; NTP, National Toxicology Program; OEHHA, Office of Environmental Health Hazard Assessment; PHG, public health goal; PoD, point of departure; RfD, reference dose; RSC, relative source contribution; SDWA, US Safe Drinking Water Act; TCP, 1,2,3-trichloropropane; TDI, tolerable daily intake; UF, uncertainty factor; US EPA, United States Environmental Protection Agency; WHO, World Health Organization.

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approximately 39% of 941 samples of groundwater (use for human consumption not specified) were found to have a median concentration of 0.7 ppb TCP (range in the 39% of samples ⩽ level of detection to 2.5 ppb). At 2 out of 10 sites in an agricultural community in New York, TCP was measured in groundwater (use unspecified) at 6 and 10 ppb (Lykins and Baier, 1985). Low levels (0.2–2 ppb) of TCP have also been detected in soils in California and Hawaii (ATSDR, 1992).

The purpose of the work presented herein is the development of a drinking water equivalent level (DWEL) for human daily consumption of TCP over a lifetime. Toward that end, a reference dose (RfD, as defined generically by US EPA (2002)) is used to establish safe levels of exposure to a chemical for exposure from all sources; for carcinogens, a RfD may also include probabilistic estimation of cancer risk when the compound of interest by default is assumed to have a linear dose–response relationship to a zero intersect based on the assumption that the compound's carcinogenicity is based on a no-threshold mode of action (MoA). A DWEL, as applied under regulations issued under the US Safe Drinking Water Act (US Congress, 1996), represents that fraction of the RfD reserved for tap water consumed directly as well as indirectly from use in food preparation.

2. Approach

The approach to estimate safe levels of exposure to TCP in drinking water includes: a critical analysis of its toxicological properties [no epidemiologic data on TCP were found in our search of the scientific literature]; an examination of data on metabolism, kinetics, and possible MoAs; an evaluation of the dose–response information to estimate toxic potency, and a description of the method used to estimate a DWEL and a RfD. The approach used herein relies on the broad construct of risk assessment embodied by the current flexible guidelines presently evinced by US EPA (2002, 2005) and the World Health Organization (WHO, 2006). The approach applies internationally recognized Frameworks for evaluating the relevance to humans of toxicological data in laboratory animals.

2.1. Hazard evaluation

The toxicity of TCP has been investigated in rats and mice using subchronic and chronic (i.e., near lifetime) durations of exposure. Three subchronic studies have been conducted in rats and one in mice; and a chronic study has been conducted in each of these two species. While findings from these studies are described below, detailed reviews of TCP's toxicology data have been prepared by ATSDR (1992), ACGIH (1996), DECOS (1998), WHO (1995, 2003), and US EPA (2009a). Relevant descriptive, kinetic, and MoA studies were critically examined, and the major findings were evaluated with a focus on determining the relevance to humans of descriptive and mechanistic investigations.

2.1.1. Non-cancer toxicity of TCP

Of the three subchronic toxicity studies of TCP in rats, one study administered TCP via drinking water, and the remainder did so via corn oil gavage (Table 1).

Male and female Sprague–Dawley rats were exposed via drinking water to TCP at 1, 10, 100, and 1000 mg/L for 13 weeks (Villeneuve et al., 1985). Drinking water intake was significantly decreased in females exposed to 100 and 1000 mg/L and in males exposed to the highest dose, likely due to reduced palatability; therefore, these animals had a reduced intake of TCP (modified doses: 17.6 at 100 mg/L and 149 mg/kg d for females and 113 mg/kg d for males at the highest concentration level). Body weight gain was significantly reduced (32% in males, 27% in females) in the highest dose for both sexes, indicating exceedance of the maximum tolerated dose (MTD). Relative liver- and kidney-to-body weight ratios were increased (6–17% liver-to-body weight, 11–31% kidney-to-body weight) significantly in females at doses 100 and 1000 mg/L. In males, liver- and kidney-to-body weight ratios were significantly increased (22–27%) in the high dose. The authors state that the increased kidney-to-body weight ratio was likely unrelated to TCP administration, because the wet weight was unaffected and the affect on the kidney:body weight ratio was assumed to be due to the decreased body weight. In the highest dose group, histopathologic changes (defined as "minor" in severity) were reported only in the liver (asinokaryosis, accentuated zonation, fatty vacuolation, and biliary hyperplasia), kidney (eosinophilic inclusions, pyknosis, nuclear displacement, fine glomerular adhesions, interstitial reactions, and proteinura), and thyroid (reduction in colloid density, follicular angular collapse, and increased epithelial height); no pancreatic acinar cell hyperplasia was reported. Increased (24–51%) clinical chemistry measures and liver enzymes (serum cholesterol in females and aminopyrine demethylase and aniline hydroxylase in males) were reported at 1000 mg/L. The study authors observed that the lowest-observed adverse effect level (LOAEL) for TCP was 149 mg/kg d (1000 mg/L) in females and 113 mg/kg d (1000 mg/L) in males. The study authors also determined a TCP dose of ~15–20 mg/kg d (100 mg/L) to be a no-observed adverse effect level (NOAEL) for males and females.

In a subchronic corn oil gavage study, male and female Sprague–Dawley rats were exposed to TCP at doses of 0, 1.5, 7.5, 15, and 59 mg/kg d (0, 0.01, 0.5, 0.1, and 0.4 mmol/kg d) for 90 days (Merrick et al., 1991). Body weights were significantly reduced (14–19%) in both sexes in the 59 mg/kg d group. In male rats, organ weights (brain, kidney, and testes) relative to body weight were significantly increased (~15–25%) in the high dose group, while the liver-to-body weight ratio was significantly increased (~13–25%) in the 15 and 59 mg/kg d groups. In females, kidney and liver weights relative to body weight were significantly increased (~8–60%) in the 15 and 59 mg/kg d groups. Increased (80–90%) concentrations of liver enzymes (Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST]) in females, but not males, in the high dose group corroborate a hepatotoxic response. While moderate changes were also seen with creatinine and blood urea nitrogen (BUN), these effects were determined by the investigators to be unrelated to dose and/or were pathologically not significant. Mild to moderate liver necrosis was reported, more frequently in male rats with increasing incidence from low to high dose, but the relevance of these effects was uncertain due to the presence of mild hepatic lesions in four control animals. Significantly increased (31–89%) serum cholesterol was also reported in female rats at doses 15 and 59 mg/kg d. Serum chemistry indicated no renal toxicity. Hyperplasia was also observed in the bile duct of both sexes in the high dose groups; based on toxicokinetic data, this effect may be due to the presence of excreted and reabsorbed stable reactive metabolites of TCP. Additionally, in both sexes at the high dose, a diffuse inflammation-associated necrosis of the cardiac myocardium was reported, indicating cardiotoxicity. We concluded a dose of 15 mg/kg d to be LOAEL for both sexes, and a dose of 7.5 mg/kg d to be a NOAEL.

In a second gavage study in 1993, the National Toxicology Program (NTP) exposed F344 rats and B6C3F1 mice to TCP via oral gavage with corn oil (doses: 0, 8, 16, 32, 63, 125, and 250 mg/kg d) for 5 days/week for 17 weeks (interim sacrifice at 8 weeks) (NTP, 1993; Irwin et al., 1995), which served as pilot investigation for subsequent carcinogenicity studies [described below].

All female rats in the high dose group died by the second week from renal or hepatic toxicity, while males in the high dose all died

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