ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR 1,2,3-TRICHLOROPROPANE

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August 2011

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ADDENDUM for 1,2,3-Trichloropropane
Supplement to the 1992 Toxicological Profile for 1,2,3-Trichloropropane

Background Statement

This addendum to the Toxicological Profile for 1,2,3-Trichloropropane supplements the profile that was released in 1992.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986, which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances, and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and federal, state, and local agencies a non-peer-reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1992.

Chapter numbers in this addendum coincide with the Toxicological Profile for 1,2,3-Trichloropropane (1992). This document should be used in conjunction with the profile; it does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.1 Death

Based on the exposure at which mortality was first observed (approximate lethal concentration, ALC) as reported in the Registry of Toxic Effects of Chemical Substances, a lethal concentration (LC_{50}) of 1000 ppm 1,2,3-trichloropropane was reported for rats (Kennedy and Graepel 1991).

2.2.1.2 Systemic Effects

Hepatic Effects. Among Chinese painters tested, the most remarkable clinical feature of occupational exposure to 1,2,3-trichloropropane (lasting 3 months to 11 years) was hepatic injury indicated by a rise in hepatic enzymes and bilirubin (Dao-yuan and Xun-miao 2008). Workers were thought to be exposed by dermal and inhalation exposure pathways because they did not wear gloves and respiratory masks on occupational sites during exposure. Dao-yuan and Xun-miao (2008) suggested that pre-existing hepatic disease may have contributed to the observed hepatic injury.

2.2.1.7 Genotoxic Effects

The number of wing spots significantly increased on the wings of heterozygous larvae of *Drosophilia melanogaster* fruit flies exposed to 4.51 µg/L 1,2,3-trichloropropane by chronic inhalation for 48 hr in 500-mL glass bottles (Chroust et al. 2007). *N*-methyl-*N*-nitrosourea and distilled water were used as the positive and negative controls, respectively. Genotoxicity was assessed using the somatic mutation and recombination test (SMART) at a concentration of 4.51 µg/L, the LC_{50} observed during toxicity testing in the third larvae instar (n = 250). The increased frequency (3.717) of total wing spots (46 small, 121 large, and 4 twin spots) induced by 1,2,3-

trichloropropane exposure was statistically significant (*p*-value not identified); the number of large spots was 2.63 times greater than the number of small spots.

2.2.2. Oral Exposure

2.2.2.1 Death

In rats (strain not specified), the lethal dose (LD_{50}) of a single dose of 1,2,3-trichloropropane was 320 mg/kg of body weight (Kennedy and Graepel 1991).

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male F344/N rats 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. Deaths were associated with hepatic or renal toxicity. All rats dosed at 250 mg/kg 1,2,3-trichloropropane died by the 5th week; one male and four females dosed at 125 mg/kg 1,2,3-trichloropropane also died during the study. No other chemical-related deaths occurred.

1,2,3-Trichloropropane was administered by corn oil gavage (3, 10, or 30 mg/kg) to 60 male and 60 female F344/N rats 5 days a week for 2 years (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. Survival rates of rats dosed at ≥ 10 mg/kg 1,2,3-trichloropropane were significantly ($p < 0.001$) lower than those of the controls. At 30 mg/kg/day female rats were moribund at week 67 and were sacrificed or died of chemical-related neoplasms of the forestomach, mammary gland, or oral mucosa between weeks 42 and 62; at 30 mg/kg/d male rats died of chemical-related neoplasms or were moribund and sacrificed during week 77 (Irwin et al. 1995; NTP 1993). Two-year survival rates of male rats were: control, 34/50; 3 mg/kg, 32/50; 10 mg/kg, 14/49; and 30 mg/kg 0/52; survival rates of female rats were: control, 31/50; 3mg/kg, 30/49; 10 mg/kg, 8/52; and 30 mg/kg, 0/52.

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male B6C3F1 mice 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. Sixteen male mice and 7 female mice dosed at 250 mg/kg 1,2,3-trichloropropane died by week 4. One additional

female mouse died the day after the last day 1,2,3-trichloropropane was administered but no other chemical-related deaths occurred.

1,2,3-Trichloropropane was administered by corn oil gavage (6, 20, or 60 mg/kg) to 60 female and 60 male B6C3F1 mice 5 days a week for 2 years (NTP, 1993). Sixty animals of each sex were given only corn oil and served as the control group. All mice dosed at ≥20 mg/kg 1,2,3-trichloropropane died due to chemical-related neoplasms. Two-year survival rates of male mice were: control, 42/52; 6 mg/kg, 18/51; 20 mg/kg, 0/54; and 60 mg/kg, 0/56; survival rates of female mice were: control, 41/50; 6 mg/kg, 13/50; 20 mg/kg, 0/51; and 60 mg/kg, 0/55.

2.2.2.2 Systemic Effects

Respiratory Effects. 1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 male and 20 female F344/N rats 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. All female and male rats dosed at 250 mg/kg 1,2,3-trichloropropane died by week 2 or week 5, respectively, and were not evaluated during the 17-week evaluation. Male rats dosed at 250 mg/kg 1,2,3-trichloropropane had significantly ($p \leq 0.01$) increased incidences of epithelial attenuation, epithelial necrosis, and acute inflammation of the nasal turbinates during an 8-week evaluation. Epithelial necrosis and chronic inflammation increased in male rats dosed at ≥ 125 mg/kg 1,2,3-trichloropropane. Chronic inflammation and epithelial attenuation increased in female rats dosed at ≥ 63 mg/kg 1,2,3-trichloropropane. Epithelial necrosis increased in females dosed at ≥125 mg/kg 1,2,3-trichloropropane. Female rats dosed at 125 mg/kg 1,2,3-trichloropropane had significantly increased incidences of epithelial attenuation ($p \leq 0.01$) of the nasal turbinates through the end of the 17-week study. Male rats dosed at 125 mg/kg 1,2,3-trichloropropane had significantly increased incidences of epithelial attenuation, epithelial necrosis, and chronic inflammation of the nasal turbinates at the end of the 17-week study.

1,2,3-trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male B6C3F1 mice 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. Female mice dosed

at 250 mg/kg 1,2,3-trichloropropane had a significantly ($p \leq 0.01$) increased incidence of lung regeneration during an 8-week evaluation. At the end of the 17-week study, female mice dosed at ≥63 mg/kg 1,2,3-trichloropropane and males dosed at ≥125 mg/kg 1,2,3-trichloropropane had a significantly ($p \leq 0.01$) increased incidence of lung/bronchiole regeneration. Lung regeneration reportedly occurred either to replace lost cells or to reline the basement membrane after damage caused by 1,2,3-trichloropropane exposure.

Cardiovascular Effects. Male and female Sprague-Dawley rats dosed daily by corn oil gavage with 0.80 mmol/kg (~118 mg/kg) 1,2,3-trichloropropane in a 10-day study or 0.1 mmol/kg (~1.5 mg/kg), 0.05 mmol/kg (~7.4mg/kg), 0.10 mmol/kg (~15mg/kg), and 0.40 mmol/kg (~59 mg/kg) 1,2,3-trichloropropane in a 90-day study sustained cardiovascular toxicity (Merrick et al. 1991). 1,2,3-Trichloropropane administered at doses of 0.01 mmol/kg/d (~1.5 mg/kg/d), 0.05 mmol/kg/d (~7.4 mg/kg/d), and 0.20 mmol/kg/d (29.5 mg/kg/d) in the 10-day study did not induce cardiovascular toxicity. Cardiac toxicity (characterized by myocardial necrosis, inflammation, and degeneration) developed in rats dosed at 0.80 mmol/kg/d (~118 mg/kg/d) 1,2,3-trichloropropane during the 10-day study; all doses in the 90-day study induced cardiac lesions and low-grade inflammation. Cardiac lesions were more prominent in male rats and increased in number and severity dose-dependently. All rats that showed cardiac toxicity also showed inflammation around the necrotic degenerating sites. Heart weight was not adversely affected by 1,2,3-trichloropropane exposure in either male or female rats. The mechanism of 1,2,3-trichloropropane cardiopathy is not known, however, the heart and the liver were the organs most sensitive to 1,2,3-trichloropropane exposure in this study.

Gastrointestinal Effects. 1,2,3-trichloropropane was administered by corn oil gavage (3, 10, or 30 mg/kg) to 60 female and 60 male F344/N rats 5 days a week for 2 years (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. Basal cell hyperplasia and squamous hyperplasia occurred in the forestomach of all rats dosed at ≥ 3 mg/kg 1,2,3-trichloropropane.

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male B6C3F1 mice 5 days a week for 8 or 17 weeks (NTP 1993). Thirty

animals of each sex were given only corn oil and served as the control group. Male mice dosed at ≥125 mg/kg 1,2,3-trichloropropane had an increased incidence of hyperkeratosis and hyperplasia of the forestomach during the 8-week and 17-week evaluations. Female mice dosed at 250 mg/kg 1,2,3-trichloropropane and ≥63 mg/kg 1,2,3-trichloropropane at the 8-week and 17-week evaluation, respectively, had a significantly increased incidence of hyperkeratosis and hyperplasia of the forestomach.

1,2,3-trichloropropane was administered by corn oil gavage (6, 20, 60 mg/kg) to 60 male and 60 female mice 5 days a week for 2 years (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. At the 15-month interim evaluation, non-neoplastic lesions or neoplasms of the forestomach occurred in mice dosed at ≥ 20 mg/kg 1,2,3-trichloropropane. Focal hyperplasia of the forestomach epithelium occurred in all groups of female mice, all male mice dosed at 6 and 60 mg/kg 1,2,3-trichloropropane, and most male mice dosed at 20 mg/kg 1,2,3-trichloropropane.

Hematological Effects. 1,2,3-Trichloropropane was administered by corn oil gavage to 20 female and 20 male F344/N rats 5 days a week for 8 or 17 weeks (8, 16, 32, 63, 125, or 250 mg/kg) (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. All female and male rats dosed at 250 mg/kg 1,2,3-trichloropropane died by week 2 or week 5, respectively, and were not evaluated during the 17-week evaluation. Erythrocyte counts decreased dose-dependently in male and female rats during an 8-week evaluation and male rats during a 17-week evaluation. Morphological erythrocyte assessment during an 8-week evaluation did not reveal an increase in polychromasia, suggesting the anemia was non-regenerative and possibly associated with a depression in erythropoiesis. Hematocrit decreased dose-dependently in male and female rats during an 8-week evaluation, all male rats during a 17-week evaluation, and female rats dosed at ≥ 32 mg/kg 1,2,3-trichloropropane during a 17-week evaluation. The decreased hematocrit may have been caused by depressed erythropoiesis or by blood loss from neoplasms in the forestomach or oral mucosa. Hemoglobin concentrations decreased dose-dependently in male rats dosed at ≥8 mg/kg 1,2,3-trichloropropane and in female rats at ≥16 mg/kg 1,2,3-trichloroproane during an 8-week evaluation and ≥8 mg/kg 1,2,3-trichloroproane during a 17-week evaluation for both male and female rats. Eosinophil counts

decreased in male rats dosed at ≥ 32 mg/kg 1,2,3-trichloropropane during an 8-week evaluation, female rats dosed at ≥ 16 mg/kg 1,2,3-trichloropropane during an 8-week evaluation, and female rats dosed at ≥ 8 mg/kg 1,2,3-trichloropropane during a 17-week evaluation.

1,2,3-Trichloropropane was administered by corn oil gavage to 60 female and 60 male F344/N rats 5 days a week for 2 years (3, 10, or 30 mg/kg) (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. Leukocyte counts and segmented neutrophils increased dose-dependently in all male and female rat dose groups during a 15-month evaluation. Hematocrit and hemoglobin decreased dose-dependently in all female groups. No significant alterations in the count of nucleated erythrocytes, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentrations at any dose in male rats were reported, although hematocrit and hemoglobin tended to decrease with dose (NTP 1993).

1,2,3-Trichloropropane was administered by corn oil gavage to 60 female and 60 male B6C3F1 mice 5 days a week for 2 years (6, 20, or 60 mg/kg) (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. Evaluations at 15 months showed chemical-related decreases in erythrocyte counts, hematocrit, and hemoglobin concentrations in male and female mice dosed at ≥ 20 mg/kg 1,2,3-trichloropropane. Decreased hematocrit may have been the result of blood loss from forestomach neoplasms or the depression of hematopoiesis. Total leukocyte counts, primarily increased numbers of segmented neutrophils, were significantly increased in all mice dosed at 60 mg/kg 1,2,3-trichloropropane. The increase in leukocyte counts was likely due to inflammation associated with chemical-induced neoplasms. No other differences in clinical chemistry parameters were considered to be associated with 1,2,3-trichloropropane administration.

Hepatic Effects. 1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 male and 20 female F344/N rats 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. All female and male rats dosed at 250 mg/kg 1,2,3-trichloropropane died by week 2 or week 5, respectively, and were not evaluated during the 17-week evaluation. The absolute and relative liver weights significantly increased in male rats dosed at ≥32 mg/kg 1,2,3-trichloropropane and

in female rats dosed at ≥16 mg/kg 1,2,3,-trichloropropane. At the 8-week interim evaluation, male rats dosed at 250 mg/kg 1,2,3-trichloropropane sustained a significantly ($p \leq 0.01$) increased incidence of liver karyomegaly and liver necrosis. Female rats dosed at ≥125 mg/kg 1,2,3-trichloropropane sustained a significantly increased incidence of liver hemorrhaging and liver necrosis. Total bilirubin values were elevated in male and female rats dosed at ≥ 63 mg/kg 1,2,3-trichloropropane, indicating increased free bilirubin production or decreased hepatocellular uptake, conjugation, or excretion of bilirubin. ALT, lactate dehydrogenase, and sorbitol dehydrogenase activity increased dose-dependently in female rats. Pseudocholinesterase activity and total bilirubin decreased dose-dependently in female rats. Pseudocholinesterase decreased dose-dependently in all male rats during the 17-week evaluation. At the end of the 17-week study, female rats dosed at 125 mg/kg 1,2,3-trichloropropane sustained a significantly ($p \leq 0.01$) increased incidence of liver necrosis and karyomegaly.

1,2,3-Trichloropropane was administered by corn oil gavage to 60 female and 60 male F344/N rats 5 days a week for 2 years (3, 10, or 30 mg/kg) (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. ALT, AST, lactate dehydrogenase, and sorbitol dehydrogenase activity decreased dose-dependently in male rats. ALT activity increased and alkaline phosphatase decreased dose-dependently in female rats. The combined incidence of hepatocellular adenoma or carcinoma was not significantly increased in any dose group, so neoplasms observed in the chronic study were not considered to be related to 1,2,3-trichloropropane administration.

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male B6C3F1 mice 5 days a week for 8 or 17 weeks (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. Absolute and relative liver rates significantly increased in female mice dosed at≥125 mg/kg 1,2,3-trichloropropane. During an 8-week evaluation, female mice dosed at 250 mg/kg 1,2,3-trichloropropane sustained a significantly ($p \leq 0.01$) increased incidence of liver necrosis. At the end of the 17-week study, male mice dosed at 250 mg/kg 1,2,3-trichloropropane had a significantly ($p \leq 0.01$) increased incidence of liver necrosis and karyomegaly. Female mice

dosed at 250 mg/kg 1,2,3-trichloropropane had a significantly ($p \leq 0.05$) increased incidence of liver necrosis at the end of 17 weeks.

1,2,3-Trichloropropane was administered by corn oil gavage to 60 female and 60 male B6C3F1 mice 5 days a week for 2 years (6, 20, or 60 mg/kg) (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. During the 15-month evaluation, nonneoplastic lesions or neoplasms of the liver occurred primarily in mice dosed at ≥ 20 mg/kg 1,2,3-trichloropropane. ALT activity increased dose-dependently in female mice and lactate dehydrogenase and sorbitol dehydrogenase increased dose-dependently in male mice.

Male and female Sprague-Dawley rats dosed daily by corn oil gavage with 0.80 mmol/kg (~118 mg/kg) 1,2,3-trichloropropane in a 10-day study or 0.1 mmol/kg (~1.5 mg/kg), 0.05 mmol/kg (~7.4mg/kg), 0.10 mmol/kg (~15mg/kg), and 0.40 mmol/kg (~59 mg/kg) 1,2,3-trichloropropane in a 90-day study sustained liver toxicity (Merrick et al. 1991). 1,2,3-Trichloropropane administered at doses of 0.01 mmol/kg/d (~1.5 mg/kg/d), 0.05 mmol/kg/d (~7.4 mg/kg/d), and 0.20 mmol/kg/d (29.5 mg/kg/d) in the 10-day study did not induce liver toxicity. Liver body weights were increased when the highest dose was administered in both studies. In the 10-day study, ALT and AST activities were elevated higher than controls for both sexes after exposure to 0.80 mmol/kg/d 1,2,3-trichloropropane. In the 90-day study, only female rats dosed at 0.40 mmol/kg/d 1,2,3-trichloropropane had elevated ALT and AST activities. In the 10-day study, centrilobular hepatic necrosis was observed in one female and two male rats dosed at 0.80 mmol/kg/d 1,2,3-trichloropropane. In the 90-day study, minimal liver necrosis was seen in one female rat dosed at 0.05 mmol/kg/d 1,2,3-trichloropropaneand two female rats dosed at 0.40 mmol/kg/d 1,2,3-trichloropropane. In the 90-day study, mild to moderate dose-related liver necrosis developed in male rats, but results were confounded by mild hepatic lesions in control animals. In the 90-day study, 40% of male and 80% of female rats dosed at 0.40 mmol/kg/d 1,2,3-trichloropropane sustained bile duct hyperplasia. In this study, the heart and the liver were the organs most sensitive to 1,2,3-trichloropropane exposure.

The adjusted liver weights of high-dose F_0 generation male and female mice significantly increased ($p < 0.05$) when 1,2,3-trichloropropane was administered by corn oil gavage to CD-1

mice at doses of 30, 60, and 120 mg/kg/d 1,2,3-trichloropropane in accordance with the Continuous Breeding Protocol in a reproductive toxicity study (NTP 1990). The adjusted liver weights of high-dose F_1 generation male and female mice significantly increased by 28% and 21%, respectively.

Male guppy fish (Poecilia reticulate; 9 mg/L) and male medaka fish (Oryzias latipes; 9 mg/L and 18 mg/L) exposed to 1,2,3-trichloropropane in tank water for 9-months and then placed in a non-contaminated tank for several months had a significantly increased incidence of bile duct hyperplasia (NTP 2005). Female medaka fish exposed in the tank for 13 months to concentrations of 4.5, 9, and 18 mg/L 1,2,3-trichloropropane also sustained a significantly increased incidence of bile duct hyperplasia.

A 45-year-old male farmer (height, 170 cm, weight 75 kg) with untreated chronic hepatitis C and a 10-year history of alcohol consumption ingested 10–15 mL of 1,2,3-trichloropropane and was subsequently diagnosed with 1,2,3-trichloropropane-induced fulminant hepatic failure at the General Hospital of Chinese People's Liberation in Beijing, China (Han 2010). Intensive treatment methods, including naloxone, pantoprazole, mannitol, rehydration, reduced glutathione, vitamin K, cefmenoxime, nutritional support, correction of acid-base imbalance, water-electrolyte disturbance, transfusion of blood plasma and irradiated platelets, etamsylate, aminomethylbenzoic acid, haemocoagulase, transfused red blood cells, red blood cell suspensions, sedatives, and dopamine, were initiated. Despite these treatment efforts, coagulation did not improve and gastrointestinal hemorrhaging continued. The patient's family chose to take the patient home after losing hope for his recovery; the hospital was unable to monitor the patient's status and treatment outcomes were unknown.

Renal Effects. 1,2,3-Trichloropropane was administered to CD-1 mice in doses of 30, 60, or 120 mg/kg/d in accordance with the Continuous Breeding Protocol in a reproductive toxicity study (NTP 1990). The kidney weights of high-dose F_0 generation female mice significantly decreased (9%), but the kidney weight of high-dose F_1 generation female mice remained unchanged; the kidney weights of F_1 generation male mice significantly increased by 14 %.

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male F344/N rats 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. All male and female rats dosed at 250 mg/kg 1,2,3-trichloropropane died by week 2 or week 5, respectively, and were not evaluated during the 17-week evaluation. Relative and absolute kidney weights were increased in all dosed rats. During an 8-week evaluation, all male and female rats dosed at ≥63 mg/kg 1,2,3-trichloropropane had a significantly ($p \leq 0.01$) increased incidence of kidney regenerative hyperplasia. The incidence of kidney karyomegaly was increased in male and female rats dosed at ≥ 125 mg/kg 1,2,3-trichloropropane and ≥ 63 mg/kg 1,2,3-trichloropropane, respectively. Kidney necrosis increased in male rats dosed at ≥ 125 mg/kg 1,2,3-trichloropropane and females dosed at 250 mg/kg 1,2,3-trichloropropane ($p \leq 0.01$). Blood urea nitrogen (BUN) levels decreased dose-dependently in all groups of male rats and in female rats dosed at ≥ 32 mg/kg 1,2,3-trichloropropane. Female rats dosed at ≥16 mg/kg 1,2,3-trichloropropane had significantly decreased creatinine concentrations. BUN levels decreased dose-dependently in female rats evaluated in the 17-week study. Creatinine concentrations decreased dose-dependently in male and female rats dosed at ≥ 16 mg/kg 1,2,3-trichloropropane during the 17-week study. At the end of the 17-week study, male and female rats dosed at 125 mg/kg 1,2,3-trichloropropane sustained a significantly ($p \leq 0.01$) increased incidence of kidney hyperplasia and karyomegaly.

1,2,3-Trichloropropane was administered by corn oil gavage (3, 10, or 30 mg/kg) to 60 female and 60 male F344/N rats 5 days a week for 2 years (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. The incidence of focal hyperplasia of the renal tubule epithelial significantly increased in male and female rats dosed at ≥10 mg/kg 1,2,3-trichloropropane. The severity of renal lesions increased with age and affected the rats dosed at 10 mg/kg 1,2,3-trichloropropane to a greater extent, perhaps due to the longer life span that group had compared with rats dosed at 30 mg/kg 1,2,3-trichloropropane. Neuropathy was characterized by degenerative changes consisting of thickening of the glomerulus and tubule basement membrane, glomerulosclerosis, degeneration and atrophy of the tubule epithelium with dilatation and cast formation, regeneration of the epithelium, interstitial fibrosis, and chronic inflammation.

Body Weight Effects. 1,2,3-Trichloropropane was administered to CD-1 mice in doses of 30, 60, and 120 mg/kg/d in accordance with the Continuous Breeding Protocol in a reproductive toxicity study (NTP 1990). Male and female mice F_0 body weights were not significantly different from controls when they were sacrificed. The body weights of male and female adult mice dosed at ≥60 mg/kg/d 1,2,3-trichloropropane in the F_1 generation increased significantly. The F_0 male and female mice dosed at ≥60 mg/kg/d 1,2,3-trichloropropane and F_1 male and female mice dosed at 120 mg/kg/d 1,2,3-trichloropropane consumed significantly more water, which may have influenced the observed weight increases.

After 90 days of gavage administration of 0.40 mmol/kg/d (~59 mg/kg/d) 1,2,3-trichloropropane, body weights of male and female rats significantly (p <0.05) decreased by 19% and 14%, respectively, compared with controls (Merrick et al. 1991). After 10 days of exposure to 0.80 mmol/kg/d (~118 mg/kg/d) 1,2,3-trichloropropane by corn oil gavage, body weights of males and females significantly (p <0.05) decreased.

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male F344/N rats 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. All female and male rats dosed at 250 mg/kg 1,2,3-trichloropropane died by week 2 or week 5, respectively, and were not evaluated during the 17-week evaluation. Body weights of male rats dosed at ≥ 63 mg/kg 1,2,3-trichloropropane and female rats dosed at 125 mg/kg 1,2,3-trichloropropane were significantly (p ≤0.01) decreased by 21% and 24%, respectively. All other dosed groups had similar final weights relative to controls.

1,2,3-Trichloropropane was administered by corn oil gavage (3, 10, or 30 mg/kg) to 60 male and 60 female F344/N rats 5 days a week for 2 years. Sixty animals of each sex were given only corn oil and served as the control group. Rats dosed at ≤10 mg/kg 1,2,3-trichloropropane maintained body weights similar to the controls throughout the study. Body weights of high-dose male rats remained at least 5% lower than body weights of the control group through sacrifice during Week 77. Body weights of the high-dose female rats remained 5% lower than

the controls after Week 58. Final body weights of rats dosed at 30 mg/kg 1,2,3-trichloropropane were 12% lower for females and 13% lower for males than those of controls (Irwin et al. 1995; NTP 1993).

1,2,3-Trichloropropane was administered by corn oil gavage (8, 16, 32, 63, 125, or 250 mg/kg) to 20 female and 20 male B6C3F1 mice 5 days a week for 8 or 17 weeks (NTP 1993). Thirty animals of each sex were given only corn oil and served as the control group. Body weights of male mice dosed at 250 mg/kg 1,2,3-trichloropropane were significantly ($p \leq 0.01$) lower than controls. All other groups of mice had body weights similar to those of controls.

1,2,3-Trichloropropane was administered by corn oil gavage (6, 20, or 60 mg/kg) to 60 male and 60 female B6C3F1 mice 5 days a week for 2 years (NTP 1993). Sixty animals of each sex were given only corn oil and served as the control group. Mean body weights of high-dose mice were consistently lower than the body weights of the control group after weeks 21 and 29 for male and female mice, respectively. Body weights of the high-dose female group remained 5% lower than the controls after Week 58. Final body weights of 60 mg/kg-dosed male and female mice were 16% and 18% of controls, respectively (Irwin 1995; NTP 1993).

2.2.2.3 Immunological and Lymphoreticular Effects

White blood cell (WBC) counts were depressed in all dose groups of male Sprague-Dawley rats dosed at 0.01 mmol/kg/d (~1.5 mg/kg/d), 0.05 mg/kg/d (~7.4 mg/kg/d), and 0.20 mmol/kg/d (29.5 mg/kg/d) and 0.80 mmol/kg/d (~118 mg/kg/d) 1,2,3-trichloropropane in a 10-day gavage study (Merrick et al. 1991). WBC counts among male rats dosed at 0.1 mmol/kg/d (~1.5 mg/kg/d), 0.05 mmol/kg/d (~7.4mg/kg/d), 0.10 mmol/kg/d (~15mg/kg/d), and 0.40 mmol/kg/d (~59 mg/kg/d) 1,2,3-trichloropropane were not affected in a corresponding 90-day study. WBC counts among female rats were not affected in the 10- or 90-day study. Male and female rats dosed at 0.80 mmol/kg/d in the 10-day study had atrophy of the thymus (characterized by loss of normal differentiation between medulla and cortex). Thymic effects receded after prolonged exposure and were not detected after the 90-day study.

2.2.2.5 Reproductive Effects

1,2,3-Trichloropropane administered by corn oil gavage to CD-1 Swiss mice (30, 60, or 120 mg/kg) according to the Continuous Breeding Protocol impaired fertility in a dose-dependent manner and was a reproductive toxicant at 120 mg/kg/d (NTP 1990). Task 1 consisted of the dose-finding study that set doses at 30, 60, and 120 mg/kg/d 1,2,3-trichloropropane. Task 2 of the study exposed male and female mice to 1,2,3-trichloropropane for a 7- and 98-day cohabitation period. Task 3 was a cross-over mating trial using the control group and the group dosed at 120 mg/kg/d 1,2,3-trichloropropane. The average number of litters per pair and the number of pups per litter significantly decreased for F_0 mice dosed at 120 mg/kg/d 1,2,3-trichloropropane. The number of epididymis sperm significantly increased in male mice dosed at 120 mg/kg/d 1,2,3-trichloropropane. The length of the estrous cycle increased significantly in all F_1-dosed female mice. Ovary weights decreased in F_0 female and F_1 mid- and high-dose female mice by 20, 15, and 40%, respectively (crossover trial). The fertility index significantly decreased in both male and female mice receiving the highest dose. The authors concluded that 1,2,3-trichloropropane is possibly a reproductive toxicant in Swiss CD-1 mice.

2.2.2.7 Genotoxic Effects

One major DNA adduct was formed *in vivo* in male B6C3F1 mice (6 or 60 mg/kg) and male Fischer-344 rats dosed once (3 or 30 mg/kg) by corn oil gavage with 1,2,3-trichloropropane and sacrificed 6 hr later (La et al. 1995). Adducts were hydrolyzed from DNA by acid hydrolysis, isolated by HPLC, and detected and quantified by radioactivity measurement. In order to characterize the initial adduct, a larger yield of adducts was produced by dosing rats with 300 mg/kg 1,2,3-trichloropropane. The isolated adduct co-eluted with the adduct derived from 1,2-dibromo-3-chloropropane (DBCP), *S*-[1-(hydroxymethyl)-2-(N^7-guanyl)-ethyl]-glutathione, indicating a shared reactive intermediate. Adducts were distributed widely and varied depending on species, organ, and dose, and were found in both target and non-target sites, indicating that factors in addition to adduct formation may be involved in carcinogenicity induced by 1,2,3-trichloropropane.

2.2.2.8 Cancer Effects

1,2,3-Trichloropropane was administered by corn oil gavage (3, 10, or 30 mg/kg) to 60 female and 60 male F344/N rats 5 days a week for 2 years (NTP 1993; Irwin et al. 1995). Sixty animals of each sex were given only corn oil and served as the control group. A 15-month interim evaluation revealed nonneoplastic lesions and neoplasms of the forestomach, oral mucosa, clitoral gland, preputial gland, mammary gland in female rats, and kidney and pancreas in male rats. In male rats dosed at ≥ 10 mg/kg 1,2,3-trichloropropane, the incidences of squamous cell papilloma of the oral mucosa, carcinoma of the oral mucosa, and adenoma of the kidney increased significantly. In male rats dosed at 30 mg/kg 1,2,3-trichloropropane, the incidence of adenoma or carcinoma (combined) of the preputial gland increased significantly. At the end of the 2-year study, the incidence of pancreatic acinar adenoma significantly increased in all dosed male rats. The incidence of squamous cell papilloma or carcinoma (combined) of the forestomach increased significantly males dosed at ≥3 mg/kg 1,2,3-trichloropropane and females dosed at ≥10 mg/kg 1,2,3-trichloropropane. In male and female rats dosed at 30 mg/kg 1,2,3-trichloropropane, the incidence of Zymbal's gland carcinoma increased significantly. In female rats dosed at ≥ 10 mg/kg 1,2,3-trichloropropane, the incidences of adenocarcinoma of the mammary gland, squamous cell papilloma, carcinoma of the oral mucosa, and adenoma or carcinoma (combined) of the clitoral gland increased significantly. Adenocarcinomas of the intestine were observed and may have been chemical related. Rats dosed at 30 mg/kg 1,2,3-trichloropropane were sacrificed at weeks 67 (females) and 77 (males) because of reduced survival attributed to chemical-related neoplasms. The LOAEL for tumors in male and female rats was determined to be 3 mg/kg/d 1,2,3-trichloropropane (Tardiff and Carson 2010). No NOAEL was identified. Results are given in TABLES 1 and 2 for male and female rats, respectively.

TABLE 1. Incidence of Nonneoplastic Lesions and Neoplasms in Male F344/N Rats

	Control	3 mg/kg	10 mg/kg	30 mg/kg
Oral mucosa[a]	60	60	59	60
Squamous cell papilloma[b]	0	4	10**	22**
Squamous cell carcinoma	1	0	11**	25**
Forestomach	60	60	59	60
Hyperplasia, basal cell	0	7*	12**	9**
Hyperplasia, squamous	3	28**	13*	6
Squamous cell papilloma	0	31**	36**	46**
Squamous cell carcinoma	0	9**	28**	14**
Pancreas	60	60	59	60
Hyperplasia	28	48**	53**	56**
Adenoma	5	21**	37**	31**
Adenocarcinoma	0	0	2	1
Kidney	60	60	59	60
Hyperplasia	0	1	23**	35**
Adenoma	0	2	20**	26**
Preuptial gland	59	57	59	58
Adenoma	5	3	6	11*
Carcinoma	0	3	3	6
Adenoma or carcinoma	5	6	9	17**

Irwin et al. (1995); NTP (1993)

[a] Number of rats per group necropsied (oral mucosa) or with tissue examined microscopically (forestomach, pancreas, kidney, preputial gland).

[b] Number of rats with lesion or neoplasm.

*,** Significantly different (*p <0.05; **p <0.01) from controls by the life table test (squamous cell carcinoma) or by logistic regression (all other lesions).

TABLE 2. Incidence of Nonneoplastic Lesions and Neoplasms in Female F344/N Rats

	Control	3 mg/kg	10 mg/kg	30 mg/kg
Oral mucosa[a]	60	59	60	60
Squamous cell papilloma[b]	1	5	10**	21**
Squamous cell carcinoma	0	1	21**	23**
Forestomach	60	59	59	60
Hyperplasia, basal cell	0	10**	5*	9**
Hyperplasia, squamous	1	26**	15**	16**
Squamous cell papilloma	0	14**	37**	24**
Squamous cell carcinoma	0	3	9**	6**
Pancreas	60	59	60	60
Hyperplasia	5	15*	24**	11**
Adenoma	0	0	2	0
Kidney	60	57	60	59
Hyperplasia	0	2	3	12**
Adenocarcinoma	0	0	0	1
Clitoral gland	56	56	58	59
Adenoma	5	11	14**	12*
Carcinoma	0	0	4	6
Adenoma or carcinoma	5	11	18**	17*
Mammary gland	60	59	60	60
Fibroadenoma or adenoma	16	23	22*	2
Adenocarcinoma	1	6	12**	22**

Irwin et al. (1995); NTP (1993)
[a] Number of rats per group necropsied (oral mucosa or mammary gland) or with tissue examined microscopically (forestomach, pancreas, kidney, clitoral gland).
[b] Number of rats with lesion or neoplasm.
*,** Significantly different (*p <0.05; **p <0.01) from controls by the life table test (squamous cell carcinoma and adenocarcinoma) or by logistic regression (all other lesions).

In an NTP (2005) study, male and female guppy fish (Poecilia reticulate) exposed to 1,2,3-trichloropropane (females, 18 mg/L; males, 4.5, 9, 18.5 mg/L) in tank water for 16 months had significantly increased incidences of hepatocellular carcinoma or adenoma (combined) (NTP 2005). Some male fish were taken out of the contaminated tank 9 months into the study and put into a non-contaminated tank for the duration of the study. Fish exposed to 18 mg/L still had a significantly increased incidence of combined hepatocellular carcinoma or adenoma. Male and female medaka fish (Oryzias latipes) exposed to a concentration of 18 mg/L of 1,2,3-trichloropropane for 13 months also had significantly increased incidences of combined hepatocellular carcinoma or adenoma.

1,2,3-Trichloropropane was administered by corn oil gavage (3, 20, or 60 mg/kg) to 60 female and 60 male B6C3F1 mice 5 days a week for 2 years (NTP 1993; Irwin et al. 1995). Sixty animals of each sex were given only corn oil and served as the control group. At the end of the two-year study, the incidences of squamous cell papilloma and carcinoma of the forestomach significantly increased in all dosed groups. In female mice dosed at 60 mg/kg 1,2,3-trichloropropane, the incidences of squamous cell carcinoma of the oral mucosa, combined hepatocellular adenoma or carcinoma, uterine adenoma, adenocarcinoma, stromal polyp, and harderian gland adenoma significantly increased. The incidence of harderian gland adenoma also significantly increased in male mice dosed at ≥20 mg/kg 1,2,3-trichloropropane. All dosed male groups had significantly increased incidences of combined hepatocellular adenoma or carcinoma. The LOAEL for tumors in male and female mice was determined to be 6 mg/kg/d 1,2,3-trichloropropane (Tardiff and Carson 2010). No NOAEL was identified. Results are given in TABLES 3 and 4 for male and female mice, respectively.

TABLE 3. Incidence of Nonneoplastic Lesions and Neoplasms in Male B6C3F1 Mice

	Control	6 mg/kg	20 mg/kg	60 mg/kg
Oral mucosa[a]	60	59	60	60
Squamous cell papilloma[b]	0	0	0	2
Forestomach	60	59	60	60
Hyperplasia, squamous	8	37**	32**	38**
Squamous cell papilloma	3	35**	25**	35**
Squamous cell carcinoma	0	41**	54**	55**
Liver	60	59	60	60
Hepatocellular adenoma	12	18	21*	31**
Hepatocellular carcinoma	4	11*	6	3
Harderian gland	60	59	60	60
Adenoma	1	2	10**	11**

Irwin et al. (1995); NTP (1993)
[a] Number of mice necropsied (oral mucosa and harderian gland) or with tissue examined microscopically (forestomach and liver).
[b] Number of mice with lesion or neoplasm
[*,**] Significantly different (*p <0.05; **p <0.01) from controls by the life table test (squamous cell carcinoma) or by logistic regression (all other lesions).

TABLE 4. Incidence of Nonneoplastic Lesions and Neoplasms in Female B6C3F1 Mice

	Control	6 mg/kg	20 mg/kg	60 mg/kg
Oral mucosa[a]	60	60	60	60
Squamous cell papilloma[b]	1	0	1	0
Squamous cell carcinoma	0	0	1	5**
Forestomach	60	60	60	60
Hyperplasia, squamous	11	25**	23**	36**
Squamous cell papilloma	0	28**	27**	33**
Squamous cell carcinoma	0	47**	55**	51**
Liver	60	60	60	60
Hepatocellular adenoma	7	9	9	36**
Hepatocellular carcinoma	1	3	0	2
Harderian gland	60	60	60	60
Adenoma	3	6	7	10*
Uterus	60	60	60	59
Stromal polyp	0	2	2	7**
Adenoma	0	1	0	4
Carcinoma	0	4**	3**	8**
Adenoma or carcinoma	0	5**	3**	12**

Irwin et al. (1995); NTP (1993)
[a] Number of mice necropsied (oral mucosa, harderian gland, or uterus) or with tissue examined microscopically (forestomach and liver).
[b] Number of mice with lesion or neoplasm
*,** Significantly different (*p <0.05; **p <0.01) from controls by the life table test (squamous cell carcinoma and uterine adenocarcinoma) or by logistic regression (all other lesions).

Carcinogenic effects were observed in Sprague-Dawley rats dosed daily by corn oil gavage at 0.80 mmol/kg/d (~118 mg/kg/d) 1,2,3-trichloropropane in a 10-day study and 0.05 mmol/kg/d (~7.4mg/kg/d) or 0.40 mmol/kg/d (~59 mg/kg/d) 1,2,3-trichloropropane in a 90-day study (Merrick et al. 1991). Doses of 0.01 mmol/kg/d (~1.5 mg/kg/d), 0.05 mmol/kg/d (~7.4 mg/kg/d), and 0.20 mmol/kg/d (29.5 mg/kg/d) 1,2,3-trichloropropane in the 10-day study and 0.01 mmol/kg/d (~1.5 mg/kg/d) and 0.10 mmol/kg/d (~15mg/kg/d) 1,2,3-trichloropropane in the 90-day study did not induce carcinogenic effects in male or female rats. Thyroid follicular adenoma was observed in one female dosed at 0.80 mmol/kg/d 1,2,3-trichloropropane in the 10-day study. A broncho-alveolar adenoma in one male rat, adenocarcinoma in one female mammary gland, forestomach squamous cell papilloma in one male, and forestomach squamous cell hyperplasia in one male were observed in rats dosed 0.40 mmol/kg/d 1,2,3-trichloropropane in the 90-day study. Hepatocellular adenoma was observed in one male dosed at 0.05 mmol/kg/d 1,2,3-trichloropropane in the 90-day study. The incidence of plasma cell hyperplasia in the

mandibular lymph nodes increased in males dosed at 118 mg/kg/d 1,2,3-trichloropropane for >10 days and in both sexes dosed at 0.40 mmol/kg/d 1,2,3-trichloropropane for >90 days**.**

Tardiff and Carson (2010) derived reference doses of 0.039 mg/kg/d and 0.014 mg/kg/d 1,2,3-trichloropropane for non-cancer and cancer endpoints, respectively, using the results from the NTP (1993). The point of derivation (POD) for the non-cancer reference dose was renal tubule hyperplasia; the POD for the cancer reference dose was combined tumors at the 50th percentile.

The International Agency for Research on Cancer (1995) classified 1,2,3-trichloropropane as "probably carcinogenic to humans" (Group 2A). The NTP (2011) classified 1,2,3-trichloropropane as "reasonably anticipated to be a carcinogen" based on clear evidence of carcinogenicity in experimental animals.

2.2.3 Dermal Exposure

2.2.3.1 Systemic Effects

Hepatic Effects. As mentioned in Section 2.2.1.2, the most remarkable clinical feature of occupational subacute 1,2,3-trichloropropane exposure (3 months to 11 years) among Chinese painters was hepatic injury indicated by a rise in hepatic enzymes and bilirubin (Dao-yuan and Xun-miao 2008). Pre-existing hepatic disease may have contributed to the observed hepatic injury. The workers were thought to be exposed by the dermal and inhalation exposure pathways because gloves and respiratory masks were not worn on occupational sites during the length of exposure.

2.2.4 Other Routes of Exposure

1,2,3-Trichloropropane administered to male Wistar rats intraperitoneally (i.p.) once in doses of 147 mg/kg, 295 mg/kg, and 442 mg/kg (1000 µmol/kg, 2000 µmol/kg, and 3000 µmol/kg, respectively) was insignificantly potent as a nephrotoxin and was not tested for testicular toxicity

because of its presumed low toxic potential (Låg 1991). It did induce single strand DNA breaks at 1,2,3-trichloropropane doses >55 mg/kg (375 µmol/kg) *in vivo*.

Male Fischer-344 rats, dosed at 3 mg/kg or 30 mg/kg 1,2,3-trichloropropane, and male B6C3F1 mice, dosed at 6 mg/kg or 60 mg/kg 1,2,3-trichloropropane, were injected i.p. with 1,2,3-trichloropropane and sacrificed 6 hr post-injection; tissue was evaluated for 1,2,3-trichloropropane-induced DNA adduct formation (La et al. 1995). Significant increases in 1,2,3-trichloropropane-induced DNA adduct formation were found in tissue previously shown (NTP 1993) to be target sites for 1,2,3-trichloropropane-induced tumor formation. However, adduct formation was also increased in tissue not previously shown to be target sites for 1,2,3-trichloropropane-induced tumor formation, indicating that 1,2,3-trichloropropane-induced carcinogenesis may not be solely a result of adduct formation.

2.3. TOXICOKINETICS

2.3.2 Distribution

2.3.2.2 Oral Exposure

1,2,3-Trichloropropane was administered once by corn oil gavage to male and female Fischer-344 rats (dosed at 30 mg/kg) and male B6C3F1 mice (dosed at 30 mg/kg and 60 mg/kg) to investigate variances in distribution (Mahmood et al. 1991). The highest concentrations of 1,2,3-trichloropropane-derived radioactivity in male rats 6 hr post-administration were in the forestomach, glandular stomach, intestine, adipose, liver, and kidney; concentrations in the adipose tissue, forestomach, glandular stomach, intestine, spleen, and lung decreased after an additional 6 hr. Concentrations were the highest in the liver, kidney, and forestomach of male and female rats 60 hr after dosing. The concentrations in female rat tissue were higher than those in male rats but significantly only in the spleen and forestomach ($p < 0.05$); concentrations in tissue 24 hr after dosing were not significantly different between male and female rats. Male mice dosed at 30 mg/kg 1,2,3-trichloropropane had significantly lower concentrations of 1,2,3-trichloropropane-derived radioactivity in the blood, liver, kidney, brain, lungs, and glandular

forestomach compared with male rats dosed at 30 mg/kg 1,2,3-trichloropropane. Male mice dosed at 60 mg/kg 1,2,3-trichloropropane had significantly higher concentrations only in the kidney and forestomach compared with male rats dosed at 30 mg/kg 1,2,3-trichloropropane. The distribution of radioactivity reportedly did not vary with dose in male mice.

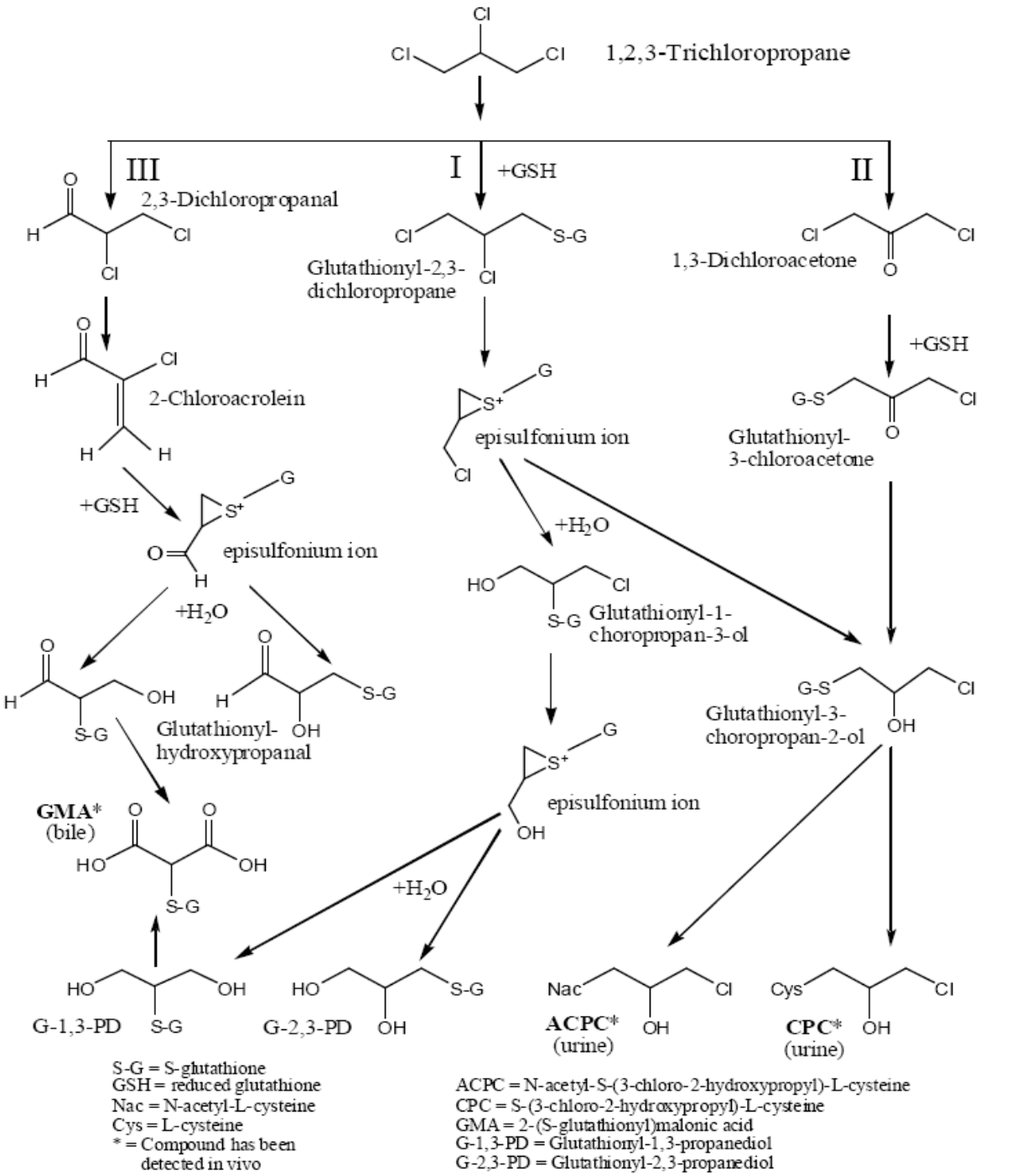
2.3.3 Metabolism

1,2,3-Trichloropropane was oxidized to both the direct acting mutagen, 1,3-dichloracetone (DCA), and 2,3-dichloropropionaldehyde, depending on which carbon oxygen insertion occurred in *Methtylosinus trichosporium* OB3b cell suspensions expressing soluble methane monooxygenase (Bosma and Janssen 1998). In an *in vitro* study by Weber and Sipes (1992), hepatic microsomes from both male F-344 rats and humans metabolized 1,2,3-trichloropropane to DCA at rates of 0.268 and 0.026 nmol/min/mg protein, respectively. Production of DCA was increased 2.5- and 24-fold by pretreating donor rats with dexamethasome and phenobarbital (PB), respectively. SKF 525-A, 1-aminobenzotriazol, and β-naphthoflavone pretreatment decreased DCA production in rat microsomes by 85%, 70%, and 50%, respectively. Alcohol dehydrogenase and NADH added to the incubation resulted in the formation of 1,3-dichloro-2-propanol and 2,3-dichloropropanol. DCA activated in microsomal incubations was able to covalently bind to microsomal protein. Pretreating donor rats with PB increased *in vitro* binding of 1,2,3-trichloropropane to microsomal protein 8-fold. Addition of glutathione (10mM) or N-acetylcysteine (10mM) prevented 1,2,3-trichloropropane from binding to protein. The only conjugate of N-acetylcysteine and 1,2,3-trichloropropane was 1,3-(2-propanone)-bis-S-(N-acetylcysteine), indicating that DCA was the major microsomal protein-binding metabolite. DCA may be responsible for the mutagenicity in rat hepatic microsomes, though its role in tumorigenicity is still unknown (Weber and Sipes 1992).

N-acetyl- and *S*-(3-chloro-2-hydroxypropyl)cysteine (ACPC and CPC) were the two urinary metabolites excreted by male and female F-344 rats at 6 hr and 24 hr post dosing by corn oil gavage with 30 mg/kg 1,2,3-trichloropropane (Mahmood et al. 1991). ACPC was the major metabolite but only accounted for ~3% of the metabolites in mouse urine. A greater number of metabolites were found in mouse urine than in rat urine. The major rat biliary metabolite was 2-(*S*-Glutathionyl)malonic acid (GMA). Biotransformation of 1,2,3-trichloropropane appears to

rely heavily on oxidation and glutathione. The metabolic pathways proposed by Mahmood et al. (1991) for 1,2,3-trichloropropane in F-344 rats are shown in the figure on the following page.

Figure 1. Proposed Metabolic Pathway for 1,2,3-Trichloropropane in F-344 Rats



(EPA 2009; Mahmood 1991; WHO 2003)

2.3.4 Excretion

2.3.4.2 Oral Exposure

Orally administered 1,2,3-trichloropropane was excreted mainly by male and female F-344 rats (30 mg/kg) and male B6C3F1 mice (30 mg/kg and 60 mg/kg) in the urine (Mahmood et al. 1991). Sixty hours after dosing, male rats, female rats, and male mice had excreted 57%, 50%, and 65%, respectively, of the 1,2,3-trichloropropane dose through urine. Exhalation as $^{14}CO_2$ and excretion in the feces each accounted for 20% of the total dose in rats, and 20% and 15%, respectively, in mice 60 hr after dosing. Male mice excreted the dose through exhalation at a faster rate than male rats, indicating a more rapid metabolism in mice. Increasing the dose to 60 mg/kg in male mice did not affect excretion. At least 90% of radioactive 1,2,3-trichloropropane was cleared 60 hr after dosing. No significant differences in routes of elimination between male and female rats or between male rats and male mice occurred.

2.4 RELEVANCE TO PUBLIC HEALTH

Genotoxicity. 1,2,3-Trichloropropane (30 mg/kg) bound covalently to hepatic proteins, RNA, and DNA in male F-344 rats (Weber and Sipes 1990a). Rats were sacrificed at 1, 4, 24, 48, and 72 hr after dosing with 1,2,3-trichloropropane (i.p), with the exception of the repeated dose study; rats in the repeated dose study were given 30 mg/kg 1,2,3-trichloropropane every 24 hr i.p. for 1, 2, or 3 doses, and sacrificed 24 hr after the last dose. 1,2,3-Trichloropropane binding to DNA decreased significantly (p <0.05) at 72 hr after dosing. 1,2,3-Trichloropropane binding to protein was the greatest at 4 hr after dosing when it was 2.5-fold greater than at 1 hr after dosing; binding decreased significantly by 24 hr after dosing. Rats dosed with phenobarbital (80 mg/kg i.p. for 4 d prior to 1,2,3-trichloropropane administration) had a significant reduction in protein-binding activity (70%), DNA-binding activity (64%), and hepatic glutathione (24%). Rats dosed at SKF 525-A (75 mg/kg i.p. 2 hr before dosing with 1,2,3-trichloropropane) had a significant increase in binding to protein (58%) and DNA (42%). B-napthofalvone did not significantly alter binding. Hepatic glutathione depletion by pretreatment with $_L$-butathione-(*R*,*S*)-sulfoximine increased binding to protein (342%) but decreased binding to DNA (44% or

56%, both results reported by Weber and Sipes (1990a). When doses of 30 mg/kg and 100 mg/kg were administered, hepatic glutathione decreased 41% and 61%, respectively. The role of glutathione in bioactivation and covalent binding is unclear.

1,2,3-Trichloropropane induced DNA hepatic damage in a dose-dependent manner as early as 1 hr after i.p. administration (30, 100, 300 mg/kg) in male F-344 rats (Weber and Sipes 1990b). Elution rate constants were significantly different relative to controls at all periods except 12 hr after dosing. DNA damage declined during the 12 hr after dosing with an increase in damage occurring at 24 hr. At 24 hr after dosing, male rats exhibited cytotoxicity indicated by increased plasma ALT activity; the increase in damage was likely due to cell degeneration and cell death. 1,2,3-Trichloropropane did not induce DNA-DNA cross links or DNA-protein cross links, although DNA appears to be the major target for 1,2,3-trichloropropane tumorigenicity.

1,2,3-Trichloropropane was genotoxic *in vitro* in the presence of S9 metabolic activation in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535 (NTP 1993). No mutagenic activity was observed in strain TA1537 with or without S9. Trifluorothymidine resistance was induced in L5178Y mouse lymphoma cells only in the presence of S9. Significantly increased sister chromatid exchanges and chromosomal aberrations induced by 1,2,3-trichloropropane were observed in cultured Chinese hamster ovary cells in the presence of S9.

In order to examine the concordance of the two genotoxicity short-term assays three hundred and thirty experimental results for the SOS chromotest using tester strain *Escherichia coli* PQ37 were compared with the results of the Salmonella microsome mutagenicity assay with *Salmonella typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and/or TA1538 (Mersch-Sundermann et al. 1994). 1,2,3-Trichloropropane was inactive in a SOS repair system test (strain PQ37) but active in a *Salmonella typhimurium* mutagenicity test (1.0 rev/nmol). A concordance of 86.4% (n = 200) was derived for the two tests (sensitivity, 78.6%; specificity, 100%; χ^2 = 188.6).

Male B6C3F1 mice administered 6 mg/kg 1,2,3-trichloropropane by gavage for 5 days developed significantly (p <0.05) greater adduct concentrations in the kidney and liver compared

with mice administered the same treatment via drinking water (La et al. 1996). Administering 1,2,3-trichloropropane via drinking water did not significantly affect cell proliferation in the liver. Proliferation in the forestomach and glandular stomach were difficult to determine due to the normal high rate of cell turnover in those organs. In a subsequent study, mice dosed at 1,2,3-trichloropropane via gavage and bromodeoxyuridine i.p. 1 hr before sacrifice had 3-fold the cell proliferation in the forestomach, glandular stomach, kidney, and liver compared with mice receiving the same treatment through drinking water. La et al. (1996) suggested that health assessments addressing toxicity tests based on gavage administration may inadequately address the toxicity of 1,2,3-trichloropropane administered in drinking water.

The induction of micronuclei by chlorinated hydrocarbons, including 1,2,3-trichloropropane, was assessed in the cytochalasin B-blocked micronucleus assay using three genetically engineered cell lines: AHH-1, h2E1, and MCL-5 (Doherty et al. 1996). 1,2,3-Trichloropropane induced a significant 8-fold increase of micronuclei in the AHH-1 and h2E1 cells lines. A significant but lower 4-fold induction of micronuclei occurred in the MCL-5 cell line, indicating the production of a metabolite less genotoxic than the parent compound. 1,2,3-Trichloropropane induced kinetochore-positive micronuclei in all three cell lines and kinetochore-negative micronuclei in the AHH-1 and h2E1 cell lines. Results indicated that 1,2,3-trichloropropane acts directly without requiring metabolic activation.

1,2,3-Trichloropropane tested negative for mutagenic activity in human lymphocytes in the presence and absence of S9 in a micronucleus assay, but tested positive for induction of DNA breakage in the presence and absence of S9 in the single cell gel electrophoresis test (comet assay) (Tafazoli and Kirsch-Volders 1996). Although the assays tested two different endpoints, Tafazoli and Kirsch-Volders (1996) suggested that the comet assay was more effective at measuring toxicity than the micronucleus assay.

1,2,3-Trichloropropane was evaluated in the mouse bone marrow micronucleus test to assess genotoxicity *in vivo* (Crebelli et al. 1999). 1,2,3-Trichloropropane (115-200 mg/kg) was administered to male and female CD-1 mice i.p. 24 hr or 48 hr before they were sacrificed. Hypoactivity, sedation, and shallow breathing were noted among the treated mice, but no

statistically significant increases in micronucleated polychromatic erythrocytes were present compared with the control values for mice treated with 1,2,3-trichloropropane or any other hydrocarbon tested. This result indicated that the mouse bone marrow micronucleus test may be only weakly sensitive to the genotoxic effects induced by halogenated hydrocarbons in several other test systems (Tafazoli and Kirsch-Volders 1996). Tafazoli and Kirsch-Volders (1996) suggested that other genotoxicity and carcinogenicity tests may be better able to characterize the toxicity of the halogenated compounds.

Nucelophilic superdelocalizability calculated by quantum mechanics was an effective parameter for predicting both the toxicity and genotoxicity of 1,2,3-trichloropropane to *Drosophila melanogaster* fruit flies (Chroust et al. 2007).

3. CHEMICAL AND PHYSICAL INFORMATION

3.2 CHEMICAL AND PHYSICAL PROPERTIES

The molecular conformation of the aliphatic chain and chlorine atoms in 1,2,3-trichloropropane is pseudo-C_2 symmetric (Podsiadlo and Katrusiak 2006). The average torsion angles are -173.4º and -60.8º at 0.28 and 0.35 GPa, respectively. The chlorine-to-chlorine bonds are the strongest bonds; the hydrogen-to-hydrogen bond distances are longer than the sum of the van der Waals radii, suggesting that chlorine-to-chlorine bonds are the determinants of the compound arrangement. Podsiadlo and Katrusiak (2006) suggested that 1,2,3-trichloropropane crystal growth rates and compressibility correspond with the strengths of intermolecular interactions in certain directions of the crystal structure.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.3 ENVIRONMENTAL FATE

5.3.2 Transformation and Degradation

Nitrosomonas europaea cell suspensions degraded 1,2,3-trichloropropane in an aerobic reaction catalyzed by ammonia oxygenase (Vannelli et al. 1990). After 24 hours in the suspensions, the remaining amount of substrate decreased from 91% to 77% after ammonia was added to the suspensions. Vannelli et al. (1990) suggested that all 1,2,3-trichloropropane would have been degraded had all of the ammonia not been consumed after 4 hr. Ammonia-oxidizing system inhibitors reduced halogenation by at least 70%, indicating the degradation was catalyzed by ammonia oxygenase.

The biodegradation of 12 chlorinated aliphatic compounds (CAC), including 1,2,3-trichloropropane, was tested in anaerobic, aerobic, and sequential-anaerobic-aerobic tests for 60, 20, and 22 days, respectively (Long et al. 1993). 1,2,3-Trichloropropane was nearly completely removed by aerobic treatment (97% by methane culture, 28% by phenol culture) but was not significantly degraded by anaerobic treatment (34%). In the sequential-aerobic bottle test, 100% of 1,2,3-trichloropropane was degraded by the methane culture and 47% by the phenol culture. Degradation was decreased in mixtures that contained 1,2,3-trichloropropane and other CACs, indicating the need for either a reduced volume of CACs or a two-part aerobic system when treating a wide range of CACs.

1,2,3-Trichloropropane was converted to products 2-chloro-1-propanol (66%), 1,3-dichloro-3-propanol (3%), 2,3-dichloro-1-propanol (11%), and chloride (62%) according to first order kinetics in resting cell suspensions of *Methylosinus trichosporium* OB3b expressing soluble methane monooxygenase (Bosma and Janssen 1998). Bosma and Janssen (1998) suggested that reductive dechlorination is a main pathway for 1,2,3-trichloropropane degradation.

Haloalkane dehalogenase taken from *Xanthobacter autotrophicus* GJ10 and *Rhodococcus* sp. M15-3 were able to dehalogenate 1,2,3-trichloropropane to 2,3-dichloro-1-propanol when expressed in *Agrobacterium radiobacter* (Bosma et al. 2002). The enzyme specificity (K_{cat}/K_m) of dehalogenase taken from *Rhodococcus* sp. M15-3 was 36 times greater than that of the dehalogenase taken from *X. autotrophicus.* Due to poor enzyme specificity, 1,2,3-trichloropropane was degraded at a much slower rate with less growth than the other substrates and could not be used as a sole carbon source.

Rhodococcus rhodochrous haloalkane dehalogenase mutants engineered by rational protein design and directed evolution had as much as 32-fold greater activity towards 1,2,3-trichloropropane than did the wild type (Pavlova et al. 2009). The most active mutant had large aromatic residues at two of three randomized positions and two positions modified by site-directed mutagenesis, decreasing the ability of water to access the active site. Engineering the mutations increased carbon-halogen bond cleavage and shifted the rate-limiting step to the release of products. Pavlova et al. (2009) suggested that modifying access routes connecting buried, active site cavities with surrounding solvents will likely increase the activity of enzymes towards anthropogenic substrates.

A second-generation mutant containing two amino acid substitutions, Cys176Tyr and Tyr273Phe, taken from a *Rhodococcus* sp. M15-3 haloalkane dehalogenase, was 8-fold and 4-fold more efficient at dehalogenating 1,2,3-trichloropropane than the wild-type dehalogenase and a dehalogenase with a single Cys176Tyr substitution, respectively (Bosma et al. 2002). The strain containing the wild-type dehalogenase converted 1.5 mM of 1,2,3-trichloropropane after 10 days. The mutated dehalogenase strand, partnering under the control of a promoter in an *Agrobacterium radiobacter* (AD1pTBS) strain containing both amino acid substitutions, converted 3.6 mM of 1,2,3-trichloropropane after 10 days and was able to use it as a sole carbon and energy source. Bosma et al. (2002) suggested that directed evolution of an enzyme and its recruitment by a suitable host can be used to construct a bacteria capable of degrading environmental 1,2,3-trichloropropane.

Two gram-negative anaerobic bacterial strains, BL-DC-8 and BL-DC-9, isolated from chlorosolvent contaminated groundwater at the PetroProcessors of Louisiana Superfund site dehalogenated 1,2,3-trichloropropane and produced the byproducts allyl chloride, allyl alcohol, diallyl sulfide, and diallyl disulfide (Yan et al. 2008). When 1,2,3-trichloropropane acted as the electron acceptor, maximum growth rates were 0.017 day^{-1} and 0.15 day^{-1}, corresponding to cell doubling times of 4.1 and 4.8 daily for BL-DC-9 and BL-DC-8, respectively. The two strains had nearly identical 16S rRNA strains placing them in the lineage of the phylum *Chloroflexi*, but the enzymes responsible for 1,2,3-trichloropropane dechlorination have not been isolated or characterized. The genus *Dehalogenimonas* and name *Dehalogenimonas lykanthroporepellens* were proposed based on phylogenetic, chemoataxonomic, and phenotypic data (Moe et al. 2009).

Fenton reagent Fe^{3+} was more effective at maximizing the biodegradability of 1,2,3-trichloropropane than Fenton reagents Fe^{2+} and F^0, but Fe^{2+} was more effective at reducing dissolved organic carbon (Khan et al. 2009). The by-products generated from Fenton degradation using reagents Fe^{2+} and Fe^{3+} on 1,2,3-trichloropropane were 1,3,-dichloro-2-propanone and 2,3-dichloro-1-propene, respectively. The by-products resulting from the use of reagent F^0, isopropanol, and propionic aldehyde have not previously been reported.

Granular Zn^0 induced faster rates of 1,2,3-trichloropropane degradation than Fe^0 without producing by-products 1,2- or 1,3-dichloropropane and 3-chloro-1-propene (Sarathy et al. 2009). Granular Zn^0 was indicated to dechlorinate mechanistically through β-elimination/hydrogenolysis. The increased Zn^0-induced reaction rates on 1,2,3-trichloropropane were semi-specific to 1,2,3-trichloropropane and may not apply to the remediation of other chlorinated solvents.

5.3.2.2 Water

A mixed culture of bacteria (*Burkholderia cepacia* G4, *B. cepacia* JS150, *Pseudomonas mendocina* KR1, *P. putida* F1, *P. putida* PaW1, and *Ralstonia pickettii* PKO1), was capable of degrading aromatic-hydrocarbons present in condensate resulting from stream classification of solid waste. This culture degraded 1,2,3-trichloropropane from 0.1 mg 1^{-1} to 0.01 mg 1^{-1} at a linear rate throughout a 4-day period (Leahy et al. 2003). The observed results indicated that

biological treatment may effectively remove volatile organic contaminants derived from stream classification.

5.3.2.3 Soil

When incubated in a sediment-slurry from a slow-moving stream near Nieuwersluis, the Netherlands, 1,2,3-trichloropropane was reductively dehalogenated until complete transformation according to zero-order kinetics with a rate constant of 0.71 (± 0.03) mmol/day was achieved (Peijnenburg et al. 1998). Degradation of 1,2,3-trichloropropane did not follow first-order kinetics, perhaps due to additional reducing agents, and was excluded from the derivation of a structure-activity relationship.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.2 Water

1,2,3-Trichloropropane was detected at concentrations occasionally exceeding 100 µg/L in water samples from 30 river and estuary sites taken at ebb tide in Osaka, Japan, from August 1993 through February 1995 (Yamamoto et al. 1997). 1,2,3-Trichloropropane was detected in all Osaka city rivers; the highest concentrations were detected in the northern part of the Osaka port in the Shorenjigawa River, a recipient of sewage effluent. Distribution was poorly defined at all sample sites.

6. ANALYTICAL METHODS

6.2 ENVIRONMENTAL SAMPLES

Additional methods for analyzing 1,2,3-trichloropropane in environmental samples not included in the 1992 Toxicological Profile for 1,2,3-trichloropropane are presented in TABLE 5.

TABLE 5. Analytical Methods for Detecting 1,2,3-Trichloropropane in Environmental Samples

Sample Matrix	Analytical Method	Detection Limit	% Recovery ± SD[c]	Reference
Ambient air samples	Short-path thermal GC-MS[a]	0.007 ppb	84% (stored samples at 1 and 6 weeks); 119 and 117% at 50% relative humidity and 90% relative humidity, respectively.	(Peng and Batterman 2000)
Ambient air samples in Montreal	EPA method TO-17	0.04 µg/m^3	No data	(Bonvalot et al. 2000)
Dutch surface waters	PT[b]/GC-MS-ion-trap	0.0004 µg/L	No data	(Miermans et al. 2000)
Water samples, Osaka, Japan	PT/ GC-MS	0.18 µg/L	No data	(Yamamoto 1997)
Drinking water	EPA method 8260b	0.32 µg/L (wide-bore capillary columns) 0.09 µg/L (narrow-bore capillary columns)	108% ± 15.6% 96% ± 6.5%	(EPA 1996)
Drinking water	GC-MS-quadruple GC-MS-ion trap Liquid-liquid extraction	0.9 ng/L 2.3 ng/L 0.8 ng/L	104% ± 5.6% 101% ± 15% 111% ± 4.8%	(California 2007)
Drinking water Groundwater	EPA method 504.1	0.02 µg/L	*Primary column:* 110.8% ± 3.69% (fortified at 0.10 µg/L) and 111.1% ± 2.13% (fortified at 0.20 µg/L) *Alternative column*: 91.9% ± 13.88 % (fortified at 0.10 µg/L) and 98.4% ± 6.36% (fortified at 0.20 µg/L).	(EPA 1985)
Drinking water Sewage water	EPA method 551.1	0.008 µg/L	88% ± 1.95%	(EPA 1990)

[a]GC-MS = Gas chromatography-Mass spectrometry
[b]PT = Purge and Trap
[c]SD = Standard deviation

7. REGULATIONS AND ADVISORIES

The NTP (2011) identified 1,2,3-trichloropropane as "reasonably anticipated to be a human carcinogen" based on clear evidence of carcinogenicity in experiment animals. It is classified as a "probable human carcinogen" by the United States Environmental Protection Agency (EPA 2009). National regulations and guidelines pertinent to human exposure to 1,2,3-trichloropropane that were developed after the publication of the 1992 Toxicological Profile for 1,2,3-trichloropropane are summarized in TABLE 6.

TABLE 6. Regulations and Guidelines for 1,2,3-Trichloropropane.

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenicity class	Group 2A[a]	(IARC 1995)
NATIONAL			
EPA	Chronic RfD (oral)	0.004 mg/kg/d	(EPA 2009)
EPA	Chronic RfC (inhalation)	0.0003 mg/m^3	(EPA 2009)
NIOSH	REL	10 ppm TWA	(NIOSH 2010)
NIOSH	IDLH concentration	100 ppm	(NIOSH 2010)
NTP	Carcinogenicity classification	Reasonably anticipated to be a carcinogen	(NTP 2011)
STATE			
California	Department of Public Health public health goal for levels in drinking water (based on cancer endpoint)	0.0007 µg/L	(California EPA, 2009)
California	Drinking water notification level	5 ng/L	(California EPA, 2009)

[a]Group 2A: probably carcinogenic to humans
EPA = Environmental Protection Agency
IARC = International Agency for Research on Cancer
IDLH = Immediate danger to life and health
NIOSH = National Institute of Occupational Safety and Health
NTP = National Toxicology Program
REL= Recommended exposure limit
RfC= Reference concentration
Rfd = Reference dose
TWA= Time-weighted Average

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