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Final Report on the Safety Assessment of Trichloroethane[1]

Trichloroethane functions in cosmetics as a solvent. Although Trichloroethane has been reported to the Food and Drug Administration (FDA) to be used in cosmetic products, an industry survey found that it is not in current use in the cosmetic industry. Trichloroethane is considered a Class I ozone-depleting substance by the Environmental Protection Agency (EPA) and its use is prohibited in the United States, unless considered essential. The FDA has stated that Trichloroethane's use in cosmetics is considered nonessential. Trichloroethane is detected by gas chromatography, gas chromatography–mass spectrometry, and gas-liquid chromatography. In rats, Trichloroethane, whether inhaled or injected, is mostly expelled intact from the body through exhalation. A very small percentage is excreted in the urine. In humans, Trichloroethane is rapidly absorbed through the skin and eliminated in exhaled air and a very small percentage is excreted in urine. Inhaled Trichloroethane is eliminated in exhaled air. Acute oral LD_{50} values have been reported as follows: 12.3 g/kg in male rats; 10.3 g/kg in female rats; 11.24 g/kg in female mice; 5.66 g/kg in female rabbits; and 9.47 g/kg in male guinea pigs. Acute toxicity studies using other routes of exposure, including subcutaneous injection and inhalation, produced no evidence of significant toxicity, except at very high exposure levels. Continuous inhalation exposure of rabbits to 750 mg/m^3 for 90 days did not produce any signs of toxicity. Continuous exposure of rats, guinea pigs, rabbits, and monkeys to 500 ppm Trichloroethane for 6 months did not produce any signs of toxicity. Other short-term and subchronic inhalation exposures confirmed acute and short-term exposure findings that the toxic effects of inhalation were a function of both concentration and time. Rats receiving 750 or 1500 mg/kg day^{-1} Trichloroethane in corn oil by oral gavage 5 days per week for 78 weeks had reduced body weights and early mortality. Reduced body weights, decreased survival rates, and early mortality (in females) were found in mice dosed with 3000 or 6000 mg/kg day^{-1} (over the last 58 weeks; lower doses were administered for the first 20 weeks). Mice exposed to prolonged periods of Trichloroethane in an inhalation chamber had increased motor activity at levels up to 5000 ppm. Further increase of concentration of exposure resulted in less of an increase of motor activity until motor activity began to fall below normal at 10,000 ppm. Adverse effects on motor activity in rats were seen at exposures as low as 3000 ppm for 4 h. Rabbits had slight reddening and scaling after 10 24-h applications to abdominal skin of Trichloroethane mixed with 2.4% to 3.0% dioxane, and slight to moderate erythema, slight edema, and slight exfoliation was observed when 75% Trichloroethane and 25% tetrachloroethylene were applied to rabbit ears for 11 days. Undiluted Trichloroethane applied to the clipped backs of guinea pigs produced histopathologic damage in the epidermis. A primary irritation index of 5.22 (out of 8) was reported in rabbits. Trichloroethane applied to the eyes of rabbits resulted in transient irritation and apparent pain, but no corneal damage. There was no effect on gestation, pup survival, or growth in mice given Trichloroethane in drinking water at up to 5.83 mg/ml during mating and/or gestation. Rats exhibited no or minimal effects of ingestion of Trichloroethane up to 30 ppm in drinking water during mating and/or gestation. There was no effect on gestation, pup survival, or growth in mice or rats inhaling 875 ppm Trichloroethane. However, prenatal exposure of rodents to Trichloroethane can produce developmental toxicity in the form of delayed development in the offspring. Trichloroethane has been found to be mutagenic in the Ames assay in some studies and not mutagenic in others. Trichloroethane induced transformations in Fischer rat embryo cell system at 99 μM, was not mutagenic using the mouse lymphoma assay at up to 0.51 μg/ml, was equivocal in that assay when tested with S9, and was also equivocal in a sister-chromatid exchange assay using Chinese hamster ovarian (CHO) cells with and without S9. Mice ingesting 80,000 ppm Trichloroethane in their drinking water had an increase in the frequency of micronucleated normochromatic erythrocytes. A peripheral blood micronucleus test in female mice was negative. Trichloroethane was not carcinogenic to rats when administered 1500 mg/kg by oral gavage 5 days/week for 78 weeks or in mice administered 6000 mg/kg. Exposure to 1500 ppm Trichloroethane vapor for 6 h/day, 5 days/week for 2 years likewise gave no indications of oncogenic effects in rats or mice. People who have been exposed to Trichloroethane have reported dizziness, lassitude, unconsciousness, respiratory depression, peripheral vascular collapse, impaired postural control, mild encephalopathy, perioral tingling, burning on the tongue and discomfort in the hands and feet. The Cosmetic Ingredient Review (CIR) Expert Panel recognizes that Trichloroethane (1,1,1-Trichloroethane) has been declared a Class I ozone-depleting substance by the EPA and its use is limited to essential products. The FDA has determined that use of Trichloroethane in aerosol cosmetic products is considered nonessential. At issue for this assessment is the safety of direct exposure to individuals as a result of exposure to cosmetic products that may contain Trichloroethane. The Expert Panel found the available data to be sufficient to support the safety of Trichloroethane as a solvent in cosmetic products.

INTRODUCTION

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, Trichloroethane (CAS nos. 71-55-6 and 25323-89-1) is described as a solvent (Gottschalck and McEwen 2006). This ingredient is the 1,1,1-Trichloroethane isomer, which should be distinguished from the 1,1,2-trichloroethane (CAS No. 79-00-5) isomer, which is not a cosmetic ingredient and is not reviewed in this safety assessment.

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In compliance with the Montreal Protocol, Title VI of the 1990 Clean Air Act prohibited the production of Trichloroethane in the United States after 1996, because it is considered a Class I ozone-depleting substance (EPA 1990).

The Clean Air Act allows exemptions from the prohibition of Trichloroethane for essential uses, medical devices, and aviation safety. However, the Food and Drug Administration (FDA) does not consider the use of Trichloroethane in an aerosol cosmetic product to be an "essential use" as described in the Clean Air Act (21CFR2.125). The use of Trichloroethane as a strictly nonaerosol cosmetic ingredient (i.e., as a solvent), however, does not fall under this prohibition. For use in other products, Trichloroethane must be obtained through other channels than production or importation, such as through recycled Trichloroethane or stocks of Trichloroethane that existed prior to 1996.

CHEMISTRY

Definition and Structure

Trichloroethane (CAS nos. 71-55-6 and 25323-89-1) is the halogenated aliphatic hydrocarbon that conforms to the formula CH_3CCl_3 (Gottschalck and McEwen 2006). As noted above, this ingredient is the 1,1,1-Trichloroethane isomer, which should be distinguished from the 1,1,2-trichloroethane (CAS no. 79-00-5) isomer, which is not a cosmetic ingredient.

Gottschalck and McEwen (2006) give the following synonyms:

- ethane 1,1,1-trichloro; methylchloroform;
- 1,1,1-trichloroethane; and
- vinyltrichloride; and these trade names:
- Aerothene TT (Dow Chemical); and
- Solvent 111 (Vulcan).

Physical and Chemical Properties

According to Reid (2001), Trichloroethane is a volatile, clear, colorless liquid that is insoluble in water. It is soluble in acetone, benzene, carbon tetrachloride, methanol, and ether. Trichloroethane is not flammable and has no flash point. Trichloroethane has a sweet chloroform-like odor that may be noticeable at air concentrations near 100 ppm, and the odor is unpleasant at 1500 to 2000 ppm. Additional chemical and physical properties of Trichloroethane are reported in Table 1.

When added to 25°C water at 1 ppm under ambient conditions, Trichloroethane evaporates rapidly, with an evaporation half-life of 20 ± 3 min (Dilling et al. 1975).

Pyrolysis of Trichloroethane at 325°C to 425°C yields 1,1-dichloroethylene and hydrogen chloride. When Trichloroethane is heated in water at 75°C to 160°C under pressure and in the presence of sulfuric acid or a metal chloride catalyst, it decomposes to acetyl chloride, acetic acid, or acetic anhydride (Snedecor 1999).

TABLE 1
Physical and chemical properties of 1,1,1-Trichloroethane.

Property	Reported value
Molecular weight	133.42
Density	1.3376 g/ml; 1.3249 g/ml
Melting point	−32.5°C; −33°C
Boiling point	74.1°C
Vapor pressure at 25°C	127 torr; 13.3 kPa
Refractive index at 21°C	1.43765
Viscosity at 20°C	0.858 mPa·s
Partition coefficient (log $K_{o/w}$)	2.68
Partition coefficient	
Water/air at 20°C	0.71
Blood/air at 20°C	1.4
Serum/air at 20°C	3.4
Specific heat at 20°C	
Liquid	1.004 J/(kg·K)
Gas	0.782 J/(kg·K)

From Budavari et al. 1989; Reid 2001; Syracuse Research Corporation 2004; Snedecor 1999; McConnell et al. 1975; Morgan et al. 1970.

Method of Manufacture

Trichloroethane is prepared by the action of chlorine on 1,1-dichloroethane (Budavari 1989). Trichloroethane is also produced by the addition of hydrochloric acid to 1,1-dichloroethylene (Budavari 1989).

McConnell et al. (1975) stated that the worldwide production of Trichloroethane in 1973 was 480,000 tons/year. Strobel and Grummt (1987) reported that the United States produced 574 million pounds (287,000 tons) of Trichloroethane in 1976. Kavaler (1989) stated that three manufacturers in the United States had the combined capacity to produce over 1 billion pounds (500,000 tons) of Trichloroethane in 1989.

Analytical Methods

Analytical methods used to detect Trichloroethane in various media include gas chromatography (GC), gas chromatography–mass spectrometry (GC-MS), and gas-liquid chromatography (GLC), as presented in Table 2.

Impurities

Hake et al. (1960) synthesized Trichloroethane in their laboratory. Analysis of the product by vapor-phase chromatography showed that the yield was 98.76% 1,1,1-Trichloroethane, 0.68% 1,1-dichloroethane, 0.36% 1,1,2-trichloroethane, and <0.1% of an uncertain compound thought to be perchloroethylene.

Reid (2001) stated that most commercially available Trichloroethane contains inhibitors to prevent reaction of the solvent with aluminum and alloys.

TABLE 2
Analytical methods used to detect Trichloroethane.

Analytical method	Matrix	Reference
GC-MS	Air	Grimsrud and Rasmussen 1975
GC-MS	Human breath, blood, urine, drinking water, and air	Barkley et al. 1980
GC-MS	Air	Pellizari 1982
GC-MS	Human blood	Antione et al. 1996
GC-MS	Human urine	Ghittori et al. 1987
GC-MS	Air, human kidney, lung, and muscle	Kroneld 1989
GC	Human blood, urine, and exhaled breath	Stewart et al. 1961
GC	Human exhaled breath	Stewart and Dodd 1964
GC	Rat exhaled breath	Boettner and Muranko 1969
GC	Rat tissues and blood	Holmberg et al. 1977
GC	Human blood, urine, and exhaled breath	Monster et al. 1979
GC	Rat blood	Schumann et al. 1982a
GC	Rat brain and blood	You and Dallas 1998
GC	Rat brain and blood	Warren et al. 2000
GLC	Rat tissues and blood	Savoleinen et al. 1977

USE

Cosmetic Use

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, Trichloroethane functions in cosmetic products as a solvent (Gottschalck and McEwen 2004). Voluntary industry reports to the U.S. Food and Drug Administration (FDA) include three reports of cosmetic products containing Trichloroethane: an aerosol hair color spray, an "other" manicuring product, and an "other" personal hygiene product (FDA 2005).

The Cosmetic Toiletry and Fragrance Association (CTFA) conducted a concentration of use survey and no company responded that Trichloroethane was used in cosmetic products (CTFA 2004). The available usage and use concentration data are given in Table 3.

Noncosmetic Use

Trichloroethane has been used as a cold solvent for metal degreasing and cleaning of electrical and electronic equipment. It is also used as a solvent in lubricants and coolants, drain cleaners, shoe polish, ink, and insecticides (Strobel and Grummt 1987).

TABLE 3
Current cosmetic product uses and concentrations for Trichloroethane.

Product category	Ingredient uses in each product category (FDA 2005)	2004 use concentrations (CTFA 2004) (%)
Hair coloring		
Color sprays	1	—
Nail care		
Other	1	—
Personal hygiene		
Other	1	—
Total uses/ranges for Trichloroethane	3	None reported

Foods

As specified in the Code of Federal Regulations (CFR), Trichloroethane may be used in formulation of adhesives used as components of articles intended for use in packaging, transporting, or holding foods (21CFR175.105) and as a cross-linking agent in polysulfide polymer–polyepoxy resins used in articles that contact dry foods (21CFR177.1650). Trichloroethane may also be used in a surgical degreaser or adhesive solvent intended to be used to dissolve surface skin oil or adhesive tape (21CFR878.4730).

McConnell et al. (1975) reported the occurrence of Trichloroethane in several foods in the United Kingdom, as detailed in Table 4.

Kroneld (1989) analyzed samples of food and beverage products from the suburbs of the city of Turku on the southwest coast

TABLE 4
Concentrations of Trichloroethane found in UK food products (McConnell et al. 1975).

Food product	Concentration (μg/kg)
English Beef (steak)	3
English Beef (fat)	6
Pig's liver	4
Olive oil (Spanish)	10
Cod liver oil	5
Castor oil	6
Tea (packet)	7
Potatoes (S. Wales)	4
Potatoes (NW England)	1
Apples	3
Pears	2
Black grapes	20
Fresh bread	2

of Finland. The products analyzed were milk, juice, coffee, fish, and meat ($n = 22$ samples of each food). Trichloroethane concentrations were not detected in any food sample (limit of detection not given).

The FDA (2003) conducted a Total Diet Study, formerly known as a Market Basket Study, in which various table-ready food products were analyzed to determine the levels of radioactive contamination, residues of pesticides, industrial chemicals, toxic and nutritional elements, and other constituents. Trichloroethane was identified in 52 food products tested. The highest concentrations of Trichloroethane were 0.0600 ppm (in raw avacado) and 0.0510 ppm (in smooth peanut butter), and the lowest concentration measured was 0.0030 ppm (in many food categories, including meats, cheeses, pastries, cookies, and ice cream).

Pharmaceuticals

By law, in the Code of Federal Regulations (CFR), all aerosol drug products intended for inhalation that contain Trichloroethane were withdrawn from the market by the FDA for reasons of safety or efficacy (21CFR216.24). Aerosol drug products containing Trichloroethane intended for human use require a new drug application (21CFR310.502).

Environmental Occurrence

Grimsrud and Rasmussen (1975) used GC-MS to analyze ambient air samples collected in a rural area of Washington state from December, 1974, to February, 1975. The Trichloroethane content of the air samples was 100 ± 15 ppt.

Barkley et al. (1980) collected samples of environmental air and water and human breath, blood, and urine in the Old Love Canal area of Niagara Falls, New York. The samples were analyzed by GC-MS for the presence of several chlorinated hydrocarbons. Trichloroethane was found in human breath from trace amounts to 2800 ppm ($n = 9$). Human blood samples contained 0.24 to 2.0 ng/ml and urine samples had 30 to 180 ng/L Trichloroethane ($n = 9$). Up to 1200 ng/m^3 Trichloroethane was found in the inside air of nine homes in the Old Love Canal area, and up to 5400 ng/m^3 Trichloroethane was found in the ambient air outside those same homes. The drinking water of those homes contained 10 to 420 ng/L Trichloroethane.

Pellizzari (1982) used GC-MS to analyze samples of ambient air collected near known industrial chemical waste disposal sites. Air samples collected near Iberville Parish, Louisiana, contained Trichloroethane concentrations ranging from trace to 8.8 ± 1.2 μg/m^3. Air samples collected near the Kin-Buc waste disposal site at Edison, New Jersey, contained from trace amounts to 120 μg/m^3 Trichloroethane.

Pellizzari et al. (1987) reported the results of a Total Exposure Assessment Methodology (TEAM) Study conducted by the EPA between 1981 and 1983. The study measured the concentrations of 20 volatile organic compounds, including Trichloroethane, in the personal air, outdoor air, drinking water, and breath of about 400 residents of New Jersey, North Carolina, and North Dakota. Table 5 summarizes the Trichloroethane concentrations detected in the TEAM study.

TABLE 5

Weighted median Trichloroethane concentrations (μg/m^3) in personal air, outdoor air, drinking water, and breath samples in New Jersey, North Carolina, and North Dakota (Pellizzari et al. 1987).

Location	Personal air	Outdoor air	Drinking water[a]	Exhaled breath
New Jersey				
Fall 1981	17	4.6	0.6	6.6
Summer 1982	9.3	5.1	0.2	5.2
Winter 1983	22	1.4	0.2	2.3
North Carolina (May, 1982)	32	60	0.03	—[b]
North Dakota (Oct., 1982)	25	0.05	0.04	9.3

[a]Mean concentration.

[b]Data uncertain based on quality assurance results.

In all cases except in North Carolina, the personal air had higher concentrations of Trichloroethane than outdoor air. No explanation was proposed for the high concentration of Trichloroethane in the North Carolina outdoor air. Occupation was the highest risk factor for having higher exposure to Trichloroethane. Employees of wood processing plants and textile plants, chemical workers, and metal workers had the highest concentrations of Trichloroethane in their personal air; however, the exact concentrations were not reported (Pellizzari et al. 1987).

Kroneld (1989) analyzed samples of ambient air from the suburbs of the city of Turku on the southwest coast of Finland. The samples were analyzed for the presence of chlorinated hydrocarbons by GC-MS. Ambient air samples contained 0.002 ± 0.001 μg/m^3 Trichloroethane ($n = 35$ samples).

Tay et al. (1995) measured Trichloroethane concentration in the air of work spaces in seven Singapore factories that use Trichloroethane for degreasing and cleaning metals. Open or manual degreasing processes generated the highest work space air concentrations of Trichloroethane, with a mean concentration of 819.9 mg/m^3 ($SD = 781.9$ mg/m^3). Jet spray cleaning produced 460.5 mg/m^3 ($SD = 292.4$ mg/m^3). Vapor degreasing produced 365.3 mg/m^3 ($SD = 279.9$ mg/m^3). Ultrasonic degreasing produced 134.7 mg/m^3 ($SD = 121.0$ mg/m^3). Blood, breath, and urine samples were collected from 50 workers in the seven factories. Levels of Trichloroethane in venous blood and exhaled breath samples taken at the end of a work shift correlated well with the work space exposure concentrations (r values of .88 and .81, respectively). Concentrations of urinary metabolites of Trichloroethane were not as strongly correlated to occupational exposure ($r = .49$ for trichloroethanol; $r = .58$ for trichloroacetic acid).

Squillace et al. (2004) tested the ground water in 19 areas across the mainland United States by sampling 518 monitoring wells between 1996 and 2002 for volatile organic compounds (VOCs). The method of analysis used was purge-and-trap, capillary column gas chromatography/mass spectrometry. Trichloroethane was in the top 14 VOCs found with a detection frequency of 23.2%. Trichlorethane had at least a 5% greater detection frequency in urban land-use areas and was among the halogenated VOCs with the largest concentrations. There was a positive population correlation as well as a positive dissolved oxygen correlation with the presence of Trichloroethane.

Huybrechts et al. (2005) tested for the presence of Trichloroethane in the southern North Sea (near France, Belgium, and The Netherlands) using GC-MS at intervals from 1998 to 2000. Results ranged from near background levels of 1 to 2 ng/L in the remote areas sampled to a mean level of 5.1 ng/L at the mouth of the Humber Estuary. The authors state that although the levels of Trichloroethane have decreased, the results are inconsistent with the assumption of near-zero emissions, the amount of time the substance has been banned and the estimated aqueous and atmospheric half-life of 1 year.

Limits for Trichloroethane in Water

The Environmental Protection Agency (EPA 2003) has set a maximum concentration level of 0.2 ppm for Trichloroethane in public water supplies. The FDA allows a maximum concentration of 0.20 mg/L Trichloroethane in bottled drinking water (21CFR165.100).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Animal

Intraperitoneal

Hake et al. (1960) gave each of three young adult white rats (two males and one female) a single intraperitoneal injection of approximately 700 mg/kg ^{14}C-Trichloroethane. The animals were then immediately placed in a metabolism cage for the collection of urine, feces, and expired breath for 25 h. The rats were then anesthetized for blood collection and killed. Samples of liver, intestine, spleen, kidney, heart, lung, brain, fat, skin, and skeletal muscle tissue were collected for analysis. All biological samples were analyzed by liquid scintillation and/or gas chromatography (GC).

The radioactivity label, at 25 h post dose, was distributed as follows: 97.6% as unchanged Trichloroethane in the expired breath, 0.5% as ^{14}C-carbon dioxide in expired breath, 0.85% in urine, including unchanged Trichloroethane and glucuronide-conjugated 2,2,2-trichloroethanol, 0.09% in skin, 0.02% in blood, 0.02% in fat, 0.03% in feces, and <0.01% in other organs. The authors stated that Trichloroethane distributed widely throughout the body with little metabolic change, no accumulation, and was rapidly eliminated primarily through exhaled breath (Hake et al. 1960).

Ikeda and Ohtsuji (1972) gave seven Wistar rats a single intraperitoneal injection of 2.78 mmol/kg Trichloroethane. Urine was collected for 48 and 96 h after the injection. Urine collected in the first 48-h period after injection contained Trichloroethane, trichloroethanol, and trichloroacetic acid corresponding to 4.0 ± 1.5, 3.5 ± 1.4, and 0.5 ± 0.2 mg/kg body weight, respectively. In the second 48-h period after injection, the respective urine concentrations of these compounds were 0.3 ± 0.1, 0 (undetectable), and 0.3 ± 0.1 mg/kg. The authors acknowledged that Trichloroethane is primarily eliminated unchanged from the lungs, but noted that trichloroethanol was the primary metabolite excreted in the urine.

Inhalation

Boettner and Muranko (1969) compared Trichloroethane levels in the exhaled breath of rats after different concentrations and durations of inhalation exposure. Male rats (strain not specified) were exposed to 100, 200, 500, or 1000 ppm Trichloroethane in an inhalation chamber for 3 h, or to 350 ppm Trichloroethane for 1, 2, 5, 10, or 20 h. Each animal's expired air was collected for analysis for 8 or 16 h after the exposure period.

The maximum concentration of Trichloroethane in the expired breath was proportional to the concentration of exposure. With the 350 ppm exposure rats followed over time, the duration of exposure did not change the amount of the compound in the breath significantly among the 5-, 10-, or 20-h exposure durations. Specific concentrations were not reported, and an elimination half-life was not calculated (Boettner and Muranko 1969).

Ikeda and Ohtsuji (1972) analyzed the urinary output of Trichloroethane and its metabolites in rats. Eight Wistar rats were exposed to 200 ppm Trichloroethane vapor in an inhalation chamber for 8 h. Urine was collected for 48 h after the exposure. The cumulative 48-h urine concentrations of Trichloroethane and its metabolites trichloroethanol and trichloroacetic acid corresponded to 3.6 ± 1.0, 3.1 ± 1.0, and 0.5 ± 0.2 mg/kg body weight, respectively.

Holmberg et al. (1977) exposed NMRI mice (3 to 10 animals/treatment) to 10 to 10,000 ppm Trichloroethane in a whole-body inhalation chamber for 0.5 to 24 h. Each animal was killed by cervical dislocation immediately after the end of its exposure period. Blood, liver, kidney, and brain tissues were collected and analyzed by GC to measure Trichloroethane content.

There was a consistent correlation between the concentration of exposure and tissue concentrations of Trichloroethane. The blood concentration and tissue concentrations of the solvent were not well correlated. When the "inspired doses" (i.e., Trichloroethane concentration in air × exposure time) were similar (same ppm × h), the liver concentrations of Trichloroethane were 10 times higher with a high solvent concentration exposure for a short time than with a low concentration exposure for a long time.

In an additional study, 10 mice were exposed to 1000 ppm Trichloroethane for 4 h and analyzed for postexposure tissue

concentrations for 2 h. The elimination rate was linear, and the biological half-life was about 20 min. In considering these studies, the authors proposed that Trichloroethane is both absorbed and eliminated through first-order kinetics (Holmberg et al. 1977).

Savolainen et al. (1977) exposed 10 male Sprague-Dawley rats to 500 ppm Trichloroethane by inhalation, 6 h per day for 4 days. On the 5th day, subsets of two rats each were exposed to the same concentration of the solvent by inhalation for 0, 2, 3, 4, or 6 h.

After 4 days of exposure, Trichloroethane accumulated in perirenal fat, with 16.9 nmol/g remaining 17 h after the fourth exposure. Small amounts of Trichloroethane (0.15 to 0.17 nmol/g) remained in the brain, lungs, and liver 17 h after the fourth exposure, and the concentration in the blood was 0.08 nmol/g. On the 5th day, concentrations of the solvent in body tissues increased with longer exposure periods. Immediately after the 6-h exposure on the 5th day, Trichloroethane concentrations in the cerebrum, cerebellum, lungs, liver, perirenal fat, and blood were 15.6, 21.3, 11.7, 21.3, 276.0, and 13.1 nmol/g, respectively (Savolainen et al. 1977).

Savolainen (1981) exposed male Wistar rats to 500 ppm Trichloroethane in an inhalation chamber 6 h per day for 5 days (number of animals was not reported). The perirenal fat of the animals killed at the above time points was analyzed to measure Trichloroethane content. During the 5th exposure, the Trichloroethane concentration in perirenal fat increased with time ($R = .99$), and the maximum concentration measured, at 6 h of exposure, was about 270 nmol/g of fat.

Schumann et al. (1982a) studied the pharmacokinetics of radiolabeled Trichloroethane in rats and mice following a single inhalation exposure. Male Fischer 344 rats and male $B6C3F_1$ mice were exposed to 150 or 1500 ppm ^{14}C-Trichloroethane for 6 h. Mice were in whole-body exposure chambers ($n = 4$ animals/species/exposure level) and rats were in head-only chambers to allow blood sample collection. Rats were housed in metabolism cages for collection of urine, feces, and expired air before and after the inhalation exposure period. Likewise, blood was collected from exposed animals before and at several time points after exposure. Additional groups of rats were exposed to the same two concentrations of Trichloroethane in a head-only chamber, so that blood could be collected during the exposure period. Seventy-two hours after the exposure, all animals were killed by cervical dislocation, and tissues were collected. All urine, feces, expired air, and tissue samples collected were analyzed by liquid scintillation to determine radioactivity content. The blood samples were analyzed by GC to measure blood concentrations of Trichloroethane.

Rats. Trichloroethane in the exhaled breath accounted for 94.2% and 97.9% of the total recovered radioactivity in the rats exposed to 150 and 1500 ppm, respectively. The remaining radioactivity in expired air (1.4% at the lower concentration and 0.7% at the higher concentration) was attributed to carbon dioxide. Urine and feces amounted to 3.4% and 0.7%, respectively, of recovered radioactivity in the 150 ppm group and 0.8% and 0.3% in the 1500 ppm group.

At termination, 72 h after exposure, 0.3% and 0.1% of the recovered radioactivity was found in the carcasses of rats exposed to 150 and 1500 ppm, respectively. At both exposure levels, the proportion of radioactivity in the body fat was 10-fold or higher than that found in other tissues such as kidney and liver. The elimination of Trichloroethane from the blood of rats was biphasic. In the initial phase, the half-life of Trichloroethane was 10.5 and 36.0 min in the 150 ppm and 1500 ppm rats, respectively. In the second phase, the half-life was 139 and 258 min for the low- and high-exposure groups, respectively.

Mice. In mice, 86.7% and 96.7% of the total recovered radioactivity was attributed to Trichloroethane in expired breath in the 150 and 1500 ppm groups, respectively. The remaining radioactivity in expired air (1.2% at the lower concentration and 0.4% at the higher concentration) was attributed to carbon dioxide. Urine and feces accounted for 8.8% and 0.8% of recovered radioactivity in the 150 ppm group and 2.3% and 0.5% in the 1500 ppm group, respectively.

At termination, 0.2% of the recovered radioactivity was found in the carcasses of mice exposed to 150 ppm Trichloroethane. At both exposure levels, the proportion of radioactivity in the body fat was 10- to 15-fold higher than that found in other tissues such as kidney and liver. The elimination of Trichloroethane from the blood of mice followed a pattern of three first-order elimination phases. In the initial phase, the half-life of Trichloroethane was 2.0 and 1.9 min in the 150 ppm and 1500 ppm mice, respectively. In the second phase, the half-life was 12.8 and 14.8 min for the low- and high-exposure groups, respectively. In the third phase, the half-life was 169 and 193 min for the low- and high-exposure levels, respectively.

Considering the pharmacokinetic profiles of rats and mice, the authors stated that the biotransformation of Trichloroethane was a saturable, dose-dependent process with little metabolism of the parent compound. The body burden and tissue and blood concentrations of inhaled Trichloroethane increased linearly with exposure in the 150 ppm to 1500 ppm range. Trichloroethanol was cleared rapidly and had little potential for bioaccumulation (Schumann et al. 1982a).

Schumann et al. (1982b) studied the pharmacokinetics of Trichloroethane in rats and mice following repeated inhalation exposures. Male Fischer 344 rats and B6C3F1 mice were exposed to 1500 ppm Trichloroethane in inhalation chambers for 6 h per day, 5 days per week, for 16 months. On the last day of exposure, radiolabeled ^{14}C-Trichloroethane was used. Another set of mice and rats were subjected to a single exposure to 1500 ppm ^{14}C-Trichloroethane for 6 h in a whole-body inhalation chamber. The animals were housed in metabolism cages for collection of urine, feces, and expired air after the inhalation exposure period. Blood was collected from exposed animals at several time points after exposure. The distribution and disposition of radioactivity was compared between single-exposure and repeated-exposure animals.

The routes of excretion and tissue concentrations of radioactivity were similar between singly and repeatedly exposed animals. ^{14}C-Trichloroethane was excreted primarily via the expired breath, constituting 97% of the total recovered radioactivity in rats and 92% to 94% in mice. The remaining radioactivity was expired as ^{14}C-carbon dioxide and nonvolatile radioactivity in the urine, feces, and cage wash. The metabolism rate of ^{14}C-Trichloroethane to ^{14}C-carbon dioxide was about 5 times higher in mice than in rats, and repeated exposure did not affect metabolism in either species. Trichloroethane did not bioaccumulate in any tissue, as radioactivity levels in kidney, liver, and fat tissues were similar between the singly and repeatedly exposed rats and mice (Schumann et al. 1982b).

Danielsson et al. (1986) studied the distribution of radiolabeled Trichloroethane in pregnant mice following inhalation exposure. Pregnant C57BL mice were exposed to 2-^{14}C-Trichloroethane for 10 min on gestation day 11, 14, or 17. The concentration of test material in air was not reported. Mice were killed for autoradiography and liquid scintillation counting immediately after the exposure period, or 30 min, 4 h, or 24 h after the exposure period. Various tissues were analyzed for the presence of radioactivity.

Immediately after a 10-min exposure to Trichloroethane, radioactivity was highest in the liver, and (in descending order) brain, lung, and kidney, with small amounts found in the placenta and fetus. The liver and kidneys remained the tissues with highest radioactivity for 24 h. Radioactivity detected in the brain, placenta, and fetus diminished rapidly after the end of exposure. Although Trichloroethane crossed the placenta into fetal tissues, there was no accumulation or retention. There was some evidence of tissue-bound metabolites of 2-^{14}C-Trichloroethane in the liver and respiratory epithelium (Danielsson et al. 1986).

You and Dallas (1998) studied the brain distribution of Trichloroethane in rats and mice following inhalation exposure. Male Sprague-Dawley rats and CD-1 mice were exposed to 3500 or 5000 ppm Trichloroethane in inhalation chambers for 10, 30, 60, or 120 min ($n = 5$ animals/species/exposure condition). Immediately after the inhalation period, blood was collected by cardiac puncture and the animals were killed for removal of the brains. Tissue samples were collected from the medulla oblongata, cerebellum, cortex, hypothalamus, striatum, midbrain, and hippocampus of the rat brain and from the medulla oblongata, cerebellum, and cortex of the mouse brains. The blood and brain tissue samples were analyzed by GC to determine Trichloroethane content.

The respective blood concentrations of Trichloroethane in rats after exposure to 3500 to 5000 ppm Trichloroethane for 10, 30, 60, and 120 min were 43.6 to 49.0, 49.4 to 50.5, 55.9 to 67.9, and 63.3 to 71.4 μg/ml; and in mice the blood concentrations were 58.9 to 66.4, 87.5 to 76.2, 92.2 to 98.8, and 101.4 to 121.3 μg/ml, respectively. The medulla oblongata had the highest concentrations of Trichloroethane in rats (182.5 to 216.7 μg/g at 120 min) and in mice (179.8 to 199.6 μg/g at 120 min). The cortex in mice (134.3 to 136.7 μg/g at 120 min) and the hippocampus in rats (105.6 to 141 μg/g at 120 min) had the lowest concentrations of Trichloroethane in the brain tissues analyzed. The authors stated that lipid content was a main factor influencing the disposition of Trichloroethane among the brain regions (You and Dallas 1998).

Warren et al. (2000) exposed Swiss-Webster mice to 500, 1000, 2000, 4000, 6000, 8000, 10,000, 12,000, or 14,000 ppm Trichloroethane by inhalation for 6, 12, 18, 24, or 30 min (4 mice/exposure condition). After each exposure period, the mice were killed, blood was drawn from the vena cava, and brains were removed. Blood and brain samples were processed and analyzed by GC. Blood and brain concentrations of Trichloroethane were fairly consistent in that μg/g brain was approximately equal to μg/ml blood. The blood concentrations at the time points and exposures tested are given in Table 6. Concentration of the solvent in blood was dependent primarily on the exposure concentration. At most exposure concentrations, the solvent levels in the blood did not increase substantially after 6 or 12 min.

TABLE 6
Blood concentrations of Trichloroethane during 30 min of inhalation exposure in mice (Warren et al. 2000).

Exposure concentration (ppm)	Blood concentration (μg/ml)* as a function of time (min)				
	6	12	18	24	30
500	8.8 ± 2.3	9.8 ± 0.8	10.7 ± 0.8	10.9 ± 0.8	10.2 ± 0.9
1000	17.5 ± 0.8	17.5 ± 1.3	20.4 ± 1.4	22.6 ± 0.9	19.6 ± 1.8
2000	25.8 ± 1.6	32.2 ± 2.9	35.4 ± 2.0	34.7 ± 1.2	37.2 ± 3.3
4000	52.6 ± 2.7	49.7 ± 8.4	52.3 ± 9.1	52.3 ± 5.4	67.2 ± 2.2
6000	60.5 ± 4.3	88.3 ± 2.9	97.6 ± 5.8	81.1 ± 8.6	96.1 ± 5.8
8000	109.7 ± 2.6	124.5 ± 9.8	120.8 ± 7.1	122.1 ± 6.1	138.1 ± 3.7
10000	137.8 ± 17.4	161.8 ± 6.7	165.3 ± 14.7	195.8 ± 20.9	204.6 ± 10.9
12000	156.0 ± 20.5	237.0 ± 23.0	224.5 ± 12.0	214.0 ± 10.0	224.5 ± 20.7
14000	195.6 ± 11.5	239.3 ± 4.6	250.8 ± 13.8	256.5 ± 14.9	257.7 ± 6.

*Values are mean ± SE ($n = 4$ mice, except at 10,000 and 14,000 ppm where $n = 2$ mice).

Human

Dermal

Stewart and Dodd (1964) studied the dermal absorption of Trichloroethane through human skin. Healthy male and female volunteers, aged 25 to 62 years, were exposed to Trichloroethane by immersion of a thumb or a hand in a container of 98% Trichloroethane, or by a topical application of an unspecified amount to the dorsal side of the hand. Each exposure duration was 30 min. Exhaled air was analyzed by GC prior to exposure and during and after exposure.

When one thumb of each of six subjects was immersed, the alveolar air concentration of Trichloroethane increased to 1 ppm at the end of exposure and decreased with a steady half-life of 1 h.

When the entire hand of one subject was immersed in Trichloroethane for 30 min, the alveolar air concentration of the solvent peaked at 21.5 ppm. The elimination half-life was about 30 min for the first 2 h and about 2.25 h thereafter.

When Trichloroethane was applied to the dorsal skin of one hand of one subject, the maximum concentration of Trichloroethane in alveolar air was 0.65 ppm. The elimination half-life was about 1.25 h. The authors concluded that in this study, Trichloroethane was rapidly absorbed through human skin and eliminated in exhaled air (Stewart and Dodd 1964).

Inhalation

Stewart et al. (1961) exposed human subjects to various concentrations of Trichloroethane in an inhalation chamber for six different exposure intervals. Concentrations of Trichloroethane in blood, urine, and exhaled breath were examined after the exposures.

Interval 1: Six subjects were exposed to 500 ppm Trichloroethane for 78 min. Analysis of blood samples collected during the exposure period showed average concentrations between 3 and 4 ppm Trichloroethane, with a range of 1.5 to 6.5 ppm. Trichloroethane was just detectable in the blood of four of the six subjects 25 min after exposure ended. Urine concentrations of the solvent peaked at 2 ppm during exposure and were at the detection limit 15 min post exposure. Trichloroethane concentrations in the expired breath were around 65 ppm at 30 min after exposure and decreased exponentially to about 3 ppm 20 h after exposure ended.

Interval 2: Six subjects were exposed to 496 ppm for 186 min. Due to contamination of the samples, analyses of the blood and urine concentrations of Trichloroethane could not be accurately performed. Ten minutes after exposure ended, the concentration of Trichloroethane in the breath was 60 ppm. The concentration in expired breath decreased exponentially to just above 1 ppm at 20 h after exposure ended.

Interval 3: Subjects were exposed to 955 ppm Tricloroethane for 73 min ($n = 3$). Subjects had maximum blood concentrations of 7 to 10 ppm Trichloroethane at the end of exposure. Blood concentrations were not reported. Maximum concentrations of Trichloroethane in expired air were 20 to 70 ppm, proportional to the exposure time. The elimination of the solvent in expired air was exponential and proportional.

Interval 4: Subjects were exposed to 910 ppm for 35 min ($n = 2$). Blood concentrations of the solvent were not reported. Trichloroethane was not detected in the urine at any time. Maximum concentrations of Trichloroethane in expired breath were 20 to 70 ppm, proportional to the exposure time. The elimination of the solvent in exhaled air was exponential and proportional.

Interval 5: Subjects were exposed to 900 ppm for 20 min ($n = 3$). Blood concentrations of the solvent were not reported. Trichloroethane was not detected in the urine at any time. Maximum concentrations of Trichloroethane in expired breath were 20 to 70 ppm, proportional to the exposure time. The elimination of the solvent in exhaled air was exponential and proportional.

Interval 6: Seven subjects were exposed to increasing concentrations from 0 to 2650 ppm over a period of 15 min. Nine minutes after exposure, blood samples contained 5 ± 1 ppm Trichloroethane, and 20 min after exposure, the concentration had fallen to 0.5 to 1 ppm. Trichloroethane was not detected in the urine of these subjects. The solvent concentration in the expired breath was 55 ppm at 20 min after exposure ended and reduced exponentially with time to 0.6 ppm at 20 h post exposure (Stewart et al. 1961).

Stewart et al. (1969) studied human exposure to Trichloroethane vapor. Volunteers were exposed to approximately 500 ppm Trichloroethane by inhalation for 6.5 to 7 h per day for 5 days. The urine of the exposed subjects was collected on each day of exposure and 12 days after the last exposure. The urine samples were analyzed by GC for the presence of the metabolites trichloroacetic acid and trichloroethanol.

The baseline mean urinary excretion rates of these two metabolites without Trichloroethane exposure were 14.2 mg/24 h and <1.0 mg/24 h, respectively. During the 5 days of exposure, the mean urinary output rates of trichloroacetic acid did not deviate much from the baseline values. After the first Trichloroethane exposure, the mean urinary output rate of trichloroethanol was 20.1 mg/24 h, and after the fourth exposure, it was 46.6 mg/24 h. By the 12th day after the last exposure, the urinary output rate of trichloroethanol was <1.0 mg/24 h.

Expired breath samples from the exposed subjects were also collected and analyzed. The decrease in breath concentrations of Trichloroethane over time was biphasic. The concentration of Trichloroethane in expired breath immediately after the last exposure was approximately 100 ppm. Elimination of the solvent was rapid in the first 12 h after the last exposure and became more gradual thereafter. The concentration of Trichloroethane in expired breath was as low as 1.0 ppm at 216 h after the last exposure (Stewart et al. 1969).

Morgan et al. (1970) studied the rate of excretion of radioactivity in exhaled breath after a single inhaled breath of radiolabeled Trichloroethane. Five human subjects each inspired a deep breath of ^{38}Cl-Trichloroethane from a closed delivery system and held it for 20 s before exhaling into a collection trap. Afterward, the subjects inhaled fresh room air and exhaled into a collection trap. The radioactivity of the exhaled air was monitored by γ-ray scintillation spectroscopy. After release of the held breath, the half-time of removal of ^{38}Cl-Trichloroethane from alveolar air was about 8 s. One hour after the single breath exposure, 44% of the inhaled dose had been exhaled.

Åstrand et al. (1973) used healthy male volunteers in a series of pharmacokinetic studies of Trichloroethane. Five subjects, aged 21 to 28 years, were exposed to 250 ppm Trichloroethane for 30 min at rest, then to 350 ppm Trichloroethane for 30 min at rest, followed by 30-min without Trichloroethane exposure. Then, each subject experienced the same pattern of exposure while engaging in physical exercise on a bicycle ergometer (50 Watt intensity). During the exposure periods, Trichloroethane vapor in air was delivered through a mouth respirator with the subject's nose pinched closed.

Trichloroethane exposures had no effect on pulmonary ventilation, oxygen uptake, heart rate, blood lactate, or electrocardiogram (ECG) parameters during exercise. Arterial, venous, and alveolar concentrations of Trichloroethane during rest increased to ~4, ~2, and ~150 ppm, respectively, during the exposure periods and returned close to baseline levels 30 min after exposure ended. With 50 Watts of exercise, the arterial, venous, and alveolar concentrations of Tichloroethane increased to ~7, ~5, and ~200 ppm, respectively. Alveolar concentrations were still elevated (~50 ppm) at 30 min after the end of exposure and returned to baseline before 310 min after exposure.

Four subjects were exposed to 250 ppm Trichloroethane for 30 min at rest, followed by about 20 min of no solvent exposure. Subjects then began to exercise at 50 Watts for about 5 min before exposure to 245 ppm Trichloroethane. After 30 min of exposure to 245 ppm with 50 Watts of exercise, the exercise intensity was increased to 100 Watts for 30 min, and then to 150 Watts for another 30 min while the 245 ppm exposure continued. Then subjects were allowed to rest and breathe fresh air while physiological parameters continued to be monitored.

Trichloroethane exposure had no effect on pulmonary ventilation, oxygen uptake, heart rate, blood lactate, or ECG parameters during exercise or at rest. Arterial, venous, and alveolar concentrations of Trichloroethane were higher during exercise, compared to the rest condition. These concentrations decreased rapidly after exposure ended. Elimination parameters such as biological half-life were not reported (Åstrand et al. 1973).

Seki et al. (1975) analyzed the urine of 196 employees of four printing factories in Germany. In factories with environmental Trichloroethane concentrations of 4 to 53 ppm, there was a linear relationship between environmental concentration of Trichloroethane and urinary concentrations of Trichloroethane, trichloroethanol, and trichloroacetic acid. When urine was collected at several time points after the end of a work shift, the biological half-life of the three trichloro-compounds was found to be about 8.7 h. When the urine of Monday-through-Friday workers was analyzed on weekends, a steady increase in trichloroethanol levels was observed throughout the 2-day weekend without Trichloroethane exposure, whereas Trichloroethane concentrations diminished and trichloroacetic acid concentrations remained unchanged. The authors suggested that these findings indicate an accumulation of Trichloroethane in the body.

Monster et al. (1979) studied the pharmacokinetics of Trichloroethane in human subjects at rest and while performing work. Six healthy male volunteers, aged 27 to 34 years, were each exposed to 70 ppm Trichloroethane for 4 h at rest, 145 ppm Trichloroethane for 4 h at rest, and 142 ppm Trichloroethane for 4 h with two 30-min periods of exercise (100 Watt workload on a bicycle ergometer). Each subject experienced each condition with an interval of 2 weeks separating the exposure sessions. Exposures to Trichloroethane were through a modified gas mask that allowed the collection of exhaled air. At the end of each exposure period, the gas mask was connected to fresh air, and the subjects kept the mask on for an additional 5 min. Blood samples were also collected 20 min before the end of the exposure period and 2, 19, 43, 67, 91, 139, and 163 h after the solvent exposure ended. Blood, urine, and exhaled air samples were analyzed by GC.

The mean cumulative uptake amounts of Trichloroethane during the 4-h exposures were 192.5 mg in the 70 ppm at rest condition, 492.2 mg in the 145 ppm at rest condition, and 537.5 mg in the 142 ppm work condition. The mean min volume of subjects exposed during rest was 10.7 L/min, and in the work condition, 30.6 L/min (minimum volumes reported include 0.3 L of physiological dead space and the dead space of the gas mask). The mean lung clearance decreased from 6.0 L/min at the beginning of exposure to 1.9 L/min after 4 h of exposure at rest. In the work condition, the mean lung clearance increased to 13.2 L/min.

In the postexposure period, the concentrations of Trichloroethane in the blood and exhaled air were well correlated, with the concentration in blood (mg/L) was consistently 8.2 times higher than in exhaled air (mg/L). Most of the absorbed Trichloroethane (62% with work and 74% to 80% at rest) was excreted unchanged by the lungs. A small amount was excreted in the urine as trichloroethanol (2%) and trichloracetic acid (1.5%). The biological half-life of Trichloroethane in these subjects ranged from 9 to 26 h (Monster et al. 1979).

BIOLOGICAL ACTIVITY

Interaction with Other Chemicals

Cornish and Adefuin (1966) studied whether ethanol potentiates the toxicity of chlorinated hydrocarbons, including Trichloroethane. Male Sprague-Dawley rats were given 0 or 5 g/kg ethanol 16 to 18 h before being placed in an inhalation

exposure chamber for exposure to 10,000 to 15,000 ppm Trichloroethane for 2 h. Additional groups of ethanol-dosed or control rats were exposed to 5000 ppm Trichloroethane for 6 h or to 10,000 ppm for 4 or 6 h. There appear to have been 14 animals in each treatment group. Clinical observations were made and blood was analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and isocitric dehydrogenase. All animals were killed 24 h after the inhalation exposure and examined at necropsy.

Serum enzymes were similar between Trichloroethane-exposed animals and control animals. There were two deaths without ethanol pretreatment and three deaths of rats in the 2-h 15,000 ppm exposure groups with ethanol pretreatment. Postmortem organ and tissue analyses revealed no signs of treatment-related toxicity. The authors concluded that ethanol did not potentiate toxicity of Trichloroethane in rats (Cornish and Adefuin, 1966).

Klaassen and Plaa (1966) studied the effect of ethanol pretreatment on the hepatic and renal toxicity of Trichloroethane using Swiss Webster mice. Animals were given 5 g/kg 60% ethanol or 0.02 ml/kg 45% dextrose solution (equicaloric control) by gavage 3 days or 12 h before receiving a single intraperitoneal injection of 2.75 ml/kg Trichloroethane. Hepatic function was measured by sulfobromophthalein (BSP) retention in the plasma and serum ALT activity. Phenolsulfonaphthalein (PSP) excretion in the urine was measured to determine renal function.

Of the parameters evaluated, only BSP retention was increased ($p < .05$) in rats given Trichloroethane 12 h or 3 days after ethanol dosing, indicating increased hepatotoxicity of Trichloroethane following ethanol exposure. Urine PSP and serum ALT activity in Trichloroethane-exposed animals were not affected by pretreatment with ethanol (Klaassen and Plaa 1966).

Cornish et al. (1973) studied the effect of phenobarbital on the hepatotoxicity of chlorinated hydrocarbons, including Trichloroethane. Male Sprague-Dawley rats were given 0 or 50 mg/kg phenobarbital intraperitoneally (i.p.) 2 days and 1 day prior to injection with 0, 0.3, 0.5, 1.0, or 2.0 mg/kg Trichloroethane. The number of animals per treatment and the route of Trichloroethane dosing were not reported. Blood was collected for analysis of serum AST levels after the first phenobarbital treatment and again after the Trichloroethane treatment. The authors stated that there was a dose-dependent increase in the serum AST levels after Trichloroethane injection, but at each dose level serum AST was not affected by pretreatment with phenobarbital.

Traiger and Plaa (1974) studied whether pretreatment with ethanol or acetone would affect the hepatotoxicity of Trichloroethane. Male Swiss-Webster mice were pretreated with 2.5 ml/kg 25% ethanol or 2.5 ml/kg 25% acetone by gavage 18 h before giving a single intraperitoneal injection of 1.0 or 1.5 ml/kg Trichloroethane in corn oil. Control groups received the Trichloroethane injections without ethanol or acetone pretreatment. Serum ALT activity was used to determine hepatic function. The authors concluded that pretreatment with ethanol or acetone did not affect serum ALT activity in mice exposed to Trichloroethane.

Hanasono et al. (1975) studied the effect of alloxan-induced diabetes on the hepatic toxicity in rats. Male Sprague-Dawley rats were pretreated with 60 mg/kg alloxan, a compound that induces diabetes by damaging beta cells in the pancreas. Three days after the alloxan pretreatment, the rats were given an intraperitoneal dose of 0 or 1.0 ml/kg Trichloroethane in 4 ml/kg corn oil. The Trichloroethane dose was selected because it was known to produce little or no elevation in serum ALT activity. The authors stated that 24 h after the solvent injection, pretreatment with alloxan had no effect on the serum ALT activity and hepatic triglyceride concentration.

Shah and Lal (1976) reported that a 24-h inhalation of 3000 ppm Trichloroethane reduced phenobarbital-induced hypnosis (loss of righting reflex) and increased hexobarbital oxidation in male mice. However, an i.p. injection of 1 ml/kg Trichloroethane increased the duration of pentobarbital-induced hypnosis and reduced hexobarbital metabolism in mice. The authors stated that these effects of i.p. injection of Trichloroethane were reduced when the vehicle was olive oil and enhanced when the vehicle was dimethylsulfoxide.

Kaneko et al. (1994) studied the effects of ethanol consumption on the metabolism of Trichloroethane in rats. Male Wistar rats were given a control liquid diet or a liquid diet containing 2 g/rat/day ethanol for at least 3 weeks. The rats were then exposed to 50, 100, or 500 ppm Trichloroethane in an inhalation chamber for 6 h. For several hours after the inhalation exposure, blood and urine samples were collected for analysis of Trichloroethane and the metabolites trichloroethanol and trichloroacetic acid.

The elimination of Trichloroethane from the blood was similar in ethanol-pretreated and control-pretreated animals. However, rats pretreated with ethanol had higher concentrations of trichloroethanol and trichloroacetic acid in the urine than the control-pretreated rats. The authors concluded that exposure to ethanol appeared to induce the enzymes that metabolize Trichloroethane without affecting the elimination rate of Trichloroethane from the blood (Kaneko et al. 1994).

Cardiovascular Effects

Rice et al. (1967) reported that the portal pressure of three male Sprague-Dawley rats was not affected by 2 ml/kg Trichloroethane, 24 h post dose. The route of exposure was not clearly reported; it was only described as an injection. The dose also had no effect on the morphology of hepatic parenchymal cells.

Clark and Tinston (1973) studied the cardiac sensitizing potential of halogenated hydrocarbons. Beagle dogs were exposed to different concentrations of volatile halogenated hydrocarbons in air delivered through a face mask for 5 min. During the last 10 s of inhalation exposure, the dogs received a bolus intravenous injection of 5 μg/kg adrenaline. Another adrenaline injection was

given 10 min after the inhalation exposure. An electrocardiogram was used to monitor cardiac function throughout the treatments. The authors defined cardiac sensitization as an increased susceptibility of the heart to catecholamine, resulting in arrhythmias such as ventricular fibrillation or ventricular tachycardia. The median effective concentration (EC_{50}) of Trichloroethane-induced cardiac sensitization was 0.75% Trichloroethane in air.

Reinhardt et al. (1973) exposed male Beagle dogs to 0.25%, 0.5%, or 1.0% (*v*/*v*) Trichloroethane in air via a face mask for 10 min (12 to 18 dogs/exposure level). Five minutes prior to and 5 min after initiation of exposure, 8 μg/kg epinephrine was given intravenously (total of 16 μg/kg epinephrine). Heart activity was monitored by electrocardiogram before, during, and after the procedure. The 0.25% Trichloroethane exposure produced no response detected by electrocardiogram in 18 dogs. Three out of 18 dogs in the 0.5% Trichloroethane group developed arrythmias. All of the 12 dogs in the 1.0% Trichloroethane group developed arrythmias, and one experienced ventricular fibrillation for several seconds before reverting to a normal rhythm.

Herd et al. (1974) performed a series of experiments to study the cardiovascular effects of Trichloroethane. Nine mongrel dogs were anesthetized with pentoparbital or chloralose/ pentobarbital and exposed to 0.8% to 2.8% Trichloroethane by inhalation for up to 5 min while several cardiovascular parameters were measured simultaneously. After the 5-min exposure, the animals were allowed to recover for 10 to 45 min. Each dog was considered recovered when the heart rate and blood pressure returned to preexposure values. Approximately 1 h after the first exposure, the dogs were exposed to similar concentrations of Trichloroethane for another 5 min while cardiovascular parameters were measured.

Trichloroethane produced a dose-dependent decrease in blood pressure. There was also a decline in the rate of change in blood pressure ($\Delta P/\Delta t$), attributed to an increase in arterial pressure rather than a direct effect on myocardial contractility. Total peripheral resistance initially declined for about 20 s but stabilized thereafter. Blood pH was reduced from 7.42 to 7.30 during exposure to 2.8% Trichloroethane. Blood pressure returned to preexposure levels 15 min after cessation of exposure, but heart rate, stroke volume, and V_{max} recovered much more slowly, up to 45 min.

Injection of 1.2 mg phenylephrine, an α-agonist, into one dog during Trichloroethane exposure reversed the course of decreased blood pressure but did not change the Trichloroethane-induced decrease in $\Delta P/\Delta t$. Heart rate decreased immediately after phenylephrine injection, but increased again after 20 s. When Trichloroethane exposure ended, the blood pressure of the phenylephrine-treated dog returned to normal more quickly than dogs not given the α-agonist. Ninety minutes after exposure to Trichloroethane and phenylephrine, the dog was exposed to Trichloroethane only for 5 min. The cardiovascular responses were similar to those seen in other dogs exposed to Trichloroethane only.

A dose of 250 μg/kg propranolol hydrochloride, a β-antagonist, given to a dog prior to Trichloroethane exposure prevented the Trichloroethane-induced increase in heart rate. Infusion of the blood of one dog with 6.1 to 6.4 mEq/L exogenous calcium (Ca^{2+}) during exposure to 2.0% Trichloroethane increased the myocardial contractility and blood pressure, compared to other dogs exposed to Trichloroethane only (Herd et al. 1974).

Belej et al. (1974) exposed Rhesus monkeys to 2.5% or 5.0% Trichloroethane in an inhalation chamber for 5 min (3 monkeys/exposure level). Exposure to 2.5% Trichloroethane decreased myocardial force and aortic blood pressure. Exposure to 5.0% Trichloroethane increased heart rate and decreased aortic blood pressure. Neither Trichloroethane concentration affected left atrial pressure or pulmonary arterial pressure.

Egle et al. (1976) fitted Beagle dogs with a telemetric electrocardiogram and exposed them to Scotchguard Brand Fabric Protector®FC-4101 at concentrations containing 5000 or 10,000 ppm Trichloroethane in an inhalation chamber for 30 min (12 and 6 dogs, respectively). Additional groups of 12 dogs received an intravenous injection of 8 or 16 μg/kg epinephrine immediately prior to a similar 5000 ppm Trichloroethane exposure. Other groups of dogs experienced a 2-s horn blast in order to induce stress immediately after the start of 5000 ppm Trichloroethane exposure (12 dogs) or a combination of the horn blast with 16 μg/kg epinephrine with 5000 ppm Trichloroethane (12 dogs). Appropriate control groups for the epinephrine and horn blast without Trichloroethane exposure were used (12 dogs/treatment group).

Heart rate was significantly increased ($p < .05$) 2, 5, and 15 min after the beginning of exposure to 5000 ppm Trichloroethane alone, compared to sham-exposure controls. The exposure to 10,000 ppm Trichloroethane alone caused a slight but nonsignificant decrease in heart rate. The heart rates of dogs receiving 8 μg/kg epinephrine, with and without the horn, were increased within 2 to 30 min of exposure to 5000 ppm Trichloroethane, compared to 8 μg/kg epinephrine controls. The heart rates of dogs receiving 16 μg/kg epinephrine, with and without the horn, were increased within 5 to 30 min of exposure to 5000 ppm Trichloroethane, compared to 16 μg/kg epinephrine controls.

Inhalation of 5000 ppm Trichloroethane did not affect the degree of arrhythmia induced by 8 or 16 μg/kg exogenous epinephrine or endogenous epinephrine, induced by horn blast (Egle et al. 1976).

Cellular Effects

Herd and Martin (1975) studied the effects of Trichloroethane on mitochondrial respiration. In vitro studies in rat liver and heart cells found that Trichloroethane inhibited mitochondrial adenosine diphosphate (ADP) respiration by interruption of electron transfer at the rotenone-sensitive site of the electron transport chain (IC_{50} = 0.65 μmoles Trichloroethane/mg mitochondrial protein). In the presence of exogenous Mg^{2+}, Trichloroethane

inhibited the production of ATP from AMP and ADP, but this inhibition did not occur without exogenous Mg^{2+}. Additionally, Trichloroethane appeared to alter the mitochondrion's permeability to Ca^{2+} and H^{+} ions. The authors proposed that these effects on mitochondrial production of ATP may explain the reduction in cardiac contractility seen in acute Trichloroethane exposures.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Torkelson et al. (1958) evaluated the single-dose toxicity of Trichloroethane and reported oral median lethal dose (LD_{50}) values of 12.3 g/kg in male rats, 10.3 g/kg in female rats, 11.24 g/kg in female mice, 5.66 g/kg in female rabbits, and 9.47 g/kg in male guinea pigs. The LD_{50} values were similar when 3.0% dioxane was added to the Trichloroethane.

Rowe et al. (1963) evaluated the single-dose toxicity of a mixture of 75% Trichloroethane and 25% tetrachloroethylene in different species and reported oral LD_{50} values of 14.8 g/kg for male and female rats, 10.3 g/kg in female mice, 5.7 g/kg in male guinea pigs, and 12.6 g/kg in male and female rabbits.

Vainio et al. (1976) gave male Wistar rats 10.3 mmol/kg Trichloroethane in olive oil by oral gavage. Twenty-four hours after the dose, the rats were killed, and the microsomal activities of NADPH cytochrome *c* reductase, cytochrome P450, epoxide hydratase, 3,4-benzpyrene hydroxylase, and *p*-nitroanisole-*O*-demethylase in the liver were measured.

Compared to control animals given only the oil vehicle, the animals given Trichloroethane had significantly reduced cytochrome P450 activity ($p < .01$) and epoxide hydratase activity ($p < .05$). The other enzyme activities were unaffected by the Trichloroethane treatment. In an additional experiment, 10.3 mmol/kg Trichloroethane by oral gavage did not affect UDP-glucuronosyltransferase activity (Vainio et al. 1976).

Acute Inhalation Toxicity

Adams et al. (1950) exposed rats to 8000 to 30,000 ppm Trichloroethane in an inhalation chamber for different durations. Fifty percent of the rats died with exposure to 18,000 ppm Trichloroethane by inhalation for 3 h or 14,250 ppm for 7 h. The deaths were attributed to cardiac or respiratory failure. Narcosis, impaired movement, ataxia, unconsciousness, irregular respiration, and loss of color in the ears and feet were observed during the exposures.

Even after the "severe" treatments of 30,000 ppm for 0.2 h and 18,000 ppm for 7 h, the surviving rats recovered from the signs of intoxication within 24 h after exposure. Necropsy conducted 24 h after exposure revealed that liver weights were higher in the rats exposed to 12,000 ppm or 8000 ppm for 7 h. The rats with increased liver weights also had slight to moderate changes in the liver upon microscopic examinations. Kidney weights were increased in rats exposed to 18,000 ppm for 2 h or 12,000 ppm for 7 h.

These authors also noted that a monkey exposed to 5000 ppm Trichloroethane by inhalation for 7 h exhibited ataxia after 1 h and trembling of the hands and forearms after 5 h. When the monkey was removed from the inhalation chamber after 7 h of exposure, its behavior was judged to be normal, and it began eating immediately (Adams et al. 1950).

Rowe et al. (1963) exposed groups of 10 rats each to various unspecified concentrations of Trichloroethane by inhalation for 1.0, 2.0, 4.0, or 7.0 h. The median lethal concentration (LC_{50}) values for the 1.0, 2.0, 4.0, and 7.0 h exposure durations were approximately 15,000, 11,000, 10,800, and 10,500 ppm Trichloroethane, respectively. An anesthetic effect was apparent during exposure, and deaths were attributed to cardiac or respiratory failure.

Gehring (1968) subjected Swiss Webster mice to a one-time exposure of 13,500 ppm Trichloroethane by inhalation for 6 to 700 min. The exposure period that killed 50% of the mice (LT_{50}) was 595 min. The median effective time (ET_{50}) of the anesthetic effect of 13,500 ppm Trichloroethane was 16.3 min. The ET_{50} of the hepatotoxic effect, as measure by increased serum alanine aminotransferase (ALT) in surviving mice, was $\geq$595 min.

Fuller at al. (1970) reported that after inhalation of 2500 to 3000 ppm Trichloroethane for 24 h, Sprague-Dawley rats had decreased duration of the narcosis effects of hexobarbital, zoxazolamine, and meprobamate. In vitro studies using the livers of the solvent-exposed rats showed increased metabolic rates for hexobarbital, zoxazolamine, and aminopyrine. Increases in the activities of microsomal *N*-demethylase activity, cytochrome P450 activity, and NADPH cytochrome *c* reductase activity were not accompanied by increases in liver weight or liver microsomal protein content. The authors stated that pretreatment of the rats with cyclohexamide or actinomycin D prevented the induction of microsomal enzymes by Trichloroethane.

Lal and Shah (1970) studied the effect of Trichloroethane inhalation on the metabolism of barbiturates. When male Swiss albino mice were exposed to 3000 ppm Trichloroethane by inhalation for 24 h, the duration of the narcosis effect of hexobarbital (80 mg/kg, i.p.) was reduced. This effect was first seen 4 h post exposure, peaked 24 h, and ended by 48 h after exposure.

The narcosis effects of barbital sodium (275 mg/kg, i.p.) and chloral hydrate (350 mg/kg, i.p.) were not affected by the Trichloroethane exposure. An 8-h exposure to 3000 ppm Trichloroethane did not effect hexobarbital-induced sleep time. Trichloroethane exposure of 3000 ppm for 24, 48, 72, or 96 h increased the rate of in vitro metabolism of hexobarbital by supernatant fractions of homogenized mouse livers ($p < .005$ for each exposure duration), without affecting the protein content (Lal and Shah 1970).

Moser and Balster (1985) reported LC_{50} values of 29,492, 20,616, and 18,358 ppm for Trichloroethane exposures of 10, 30, and 60 min, respectively, in male CD-1 mice.

Acute Intraperintoneal Toxicity

Plaa et al. (1958) reported a subcutaneous LD_{50} value of 120 mM/kg Trichloroethane in albino male mice. Trichloroethane prolonged the pentobarbital-induced (45 mg/kg of 2% sodium pentobarbital) sleep time with an ED_{50} of 84 mM/kg. In this study, pentobarbital-induced sleep time was used as a measure of hepatic dysfunction, as Trichloroethane inhibited the normal metabolism of sodium pentobarbital. Hepatotoxicity was also measured by retention of bromosulfalein in the plasma. The bromosulfalein retention rates were 2/9 (animals effects/animals tested) and 10/10 with subcutaneous doses of 78 and 120 mM/kg Trichloroethane. Thus, pentobarbital-induced sleep time was determine to be a more sensitive method of determining the hepatoxicity of Trichloroethane than bromosulfalein retention.

Plaa and Larson (1965) gave Swiss mice a single intraperitoneal injection of 2.5 or 5 ml/kg Trichloroethane (nine and three animals, respectively). Twenty-four hours after the injection, renal function was measured by a PSP excretion assay, determination of protein and glucose in the urine, and by microscopic examination. One of the nine mice (11%) given 2.5 ml/kg Trichloroethane had increased protein in the urine. Glucose and PSP excretion were not affected by Trichloroethane exposure. Swelling of the proximal convoluted tubules was observed in five out of five mice evaluated by microscopic analysis of the kidneys.

Klaassen and Plaa (1966) reported a 24-h LD_{50} of 3.8 ml/kg (37 mmol/kg) Trichloroethane by intrapertoneal injection in male Swiss-Webster mice. BSP retention and serum alanine aminotransferase (ALT) were used as measures of hepatotoxicity. The median effective dose (ED_{50}) values of increased BSP retention and increased serum ALT were 2.8 and 2.5 ml/kg, respectively. Other hepatic observations included enlargement of hepatocytes with cellular infiltration and vacuolation and slight necrosis only in the lethal dose range. No microscopic damage in the kidneys was observed in animals treated with Trichloroethane.

Klaassen and Plaa (1967) reported a 24-h LD_{50} of 3.1 ml/kg (31 mmol/kg) Trichloroethane by intraperitoneal injection in mongrel dogs. Trichloroethane exposure increased serum ALT levels with an ED_{50} of 0.87 ml/kg. On microscopic evaluation of the liver of surviving dogs, there was moderate neutrophlic infiltrations in the sinusoids and portal areas, but no necrosis. Slight calcification was seen in the renal tubules of the treated dogs.

Gehring (1968) reported a 24-h LD_{50} of intraperitoneal injections of Trichloroethane of 35.2 mmol/kg in Swiss-Webster Mice. Trichloroethane increased ALT with an ED_{50} of 21.8 mmol/kg. The ratio of LD_{50} to ED_{50} in this study was 1.62.

Klaassen and Plaa (1969) treated male Sprague-Dawley rats with 2.8 ml/kg Trichloroethane by i.p. injection and later measured liver triglycerides, glucose-6-phosphatase activity, and lipid peroxidation. Trichloroethane did not affect any of these parameters. The LD_{50} was 3.8 ml/kg.

Short-Term Oral Toxicity

Platt and Cockrill (1969) treated rats with 1650 mg/kg day^{-1} Trichloroethane by oral gavage for seven days. The rats were later examined for signs of liver toxicity. Liver weights, cytochrome *c* reductase activity, glucose-6-phosphatase activity, lactate dehydrogenase activity, glucose-6-phosphate dehydrogenase activity, and 15-hydroxyprostaglandin dehydrogenase activity were not affected by the Trichloroethane treatment. However, the solvent treatment increased microsomal protein concentration ($p < .01$), increased cell-sap protein concentration ($p < .01$), increased cytochrome *c* reductase activity, and increased glutamate dehydrogenase activity ($p < .1$).

The National Toxicology Program (NTP) treated male F344/N rats with 0, 0.62, or 1.24 mmol/kg day^{-1} Trichloroethane by oral gavage for 3 weeks ($n = 5$ rats/dose level). Final body weights and body weight gains were not affected by the Trichloroethane treatment, and there were no clinical signs of toxicity. The relative liver weights of rats in the 2.4 mmol/kg/day group were slightly greater than seen in control animals. The urinary protein output and serum AST activity were increased in the 2.4 mmol/kg day^{-1} group. There was no microscopic evidence of damage to the kidney or liver. The lowest observed effect level (LOEL) of Trichloroethane was 0.62 mmol/kg in this study (NTP 1996).

NTP (2000) treated male and female F344/N rats with 5000, 10,000, 20,000, 40,000, or 80,000 ppm Trichloroethane administered in microcapsules in feed for 13 weeks ($n = 10$ rats/sex/exposure level). Based on average food consumption, the estimated Trichloroethane consumption rates were 300, 600, 1200, 2400, and 4800 mg/kg/day for males and 300, 650, 1250, 2500, and 5000 mg/kg/day for females in the 5000, 10,000, 20,000, 40,000, or 80,000 ppm groups, respectively.

All rats survived to the end of the treatment period. Changes in clinical pathology parameters were minor, inconsistent, and considered unrelated to Trichloroethane exposure. Female rats exposed to 80,000 ppm Trichloroethane had decreased liver weights. Male rats exposed to 10,000 to 80,000 ppm Trichloroethane had non-neoplastic kidney lesions consistent with hyaline droplet nephropathy. No treatment-related microscopic lesions were observed in female rats.

In a related study, male and female B6C3F1 mice received 5000, 10,000, 20,000, 40,000, or 80,000 ppm Trichloroethane administered in microcapsules in feed for 13 weeks ($n = 10$ mice/sex/exposure level). Based on average food consumption, the estimated Trichloroethane consumption rates were 850, 1770, 3500, 7370, and 15,000 mg/kg day^{-1} for males and 1340, 2820, 5600, 11,125, and 23,000 mg/kg day^{-1} for females in the 5000, 10,000, 20,000, 40,000, or 80,000 ppm groups, respectively.

There were no treatment-related deaths in the mouse study. Male and female mice of the 20,000 to 80,000 ppm groups had decreased body weights during the study. No biologically significant differences in organ weights were observed between treated

and control mice. No gross microscopic lesions attributable to treatment were observed (NTP 2000).

Short-Term Inhalation Toxicity

Adams et al. (1950) studied the toxicity of repeated 7-h inhalation exposures to Trichloroethane in different species. Five male and five female guinea pigs were exposed to 5000 ppm Trichloroethane by inhalation for 7 h per day, 32 days in a 45-day period. Initially, weight loss was seen in the treated groups, but later in the experiment weight gain was noted. Final body weights of treated animals were lower than those of control animals. The treated guinea pigs had slight to moderate central fatty degeneration of the liver without signs of necrosis. Male guinea pigs had varying degrees of testicular degeneration not seen in control animals. Although no microscopic changes were observed in the kidneys, blood urea nitrogen (BUN) was lower in the exposed animals (BUN = 25.9 mg/ml), compared to control animals (BUN = 28.6 mg/ml).

Five male and four female guinea pigs were exposed to 3000 ppm Trichloroethane by inhalation for 7 h per day, 20 days in a 29-day period. Body weight gains of exposed animals were lower than controls. The treated guinea pigs had slight central fatty degeneration of the liver, and oil red O staining revealed small but distinct globules in the central zone of hepatic lobules. No other signs of toxicity were noted.

Twelve male and eight female guinea pigs were exposed to 1500 ppm Trichloroethane by inhalation for 7 h per day, 44 days in a 60-day period. The only observation in the treated animals was decreased weight gain in both sexes.

Nine male and 10 female guinea pigs were exposed to 650 ppm Trichloroethane by inhalation for 7 h per day, 65 days in a 93-day period. Additional groups of eight male and six female guinea pigs were exposed to 650 ppm Trichloroethane by inhalation for 7 h per day, 41 days in a 58-day period. Weight gain was reduced in treated animals, but no other toxicological observations were reported.

Five male and five female rats were exposed to 0 or 5000 ppm Trichloroethane by inhalation for 7 h per day, 31 days in a 44-day period. Aside from unsteadiness and lethargy when they were removed from the inhalation chamber, the exposed rats showed no signs of toxicity. Findings in gross necropsy, microscopic analysis, and BUN analysis were all normal.

Five male and five female rats were exposed to 3000 ppm Trichloroethane by inhalation for 7 h per day, 47 days in a 67-day period. No signs of toxicity were observed.

Two female rabbits were exposed to 5000 ppm Trichloroethane by inhalation for 7 h per day, 31 days in a 44-day period. Exposed animals had slightly retarded growth, compared to controls, but no other signs of toxicity were observed. Clinical and postmortem analyses were normal.

A female monkey was exposed to 3000 ppm Trichloroethane by inhalation for 7 h per day, 53 days in a 74-day period. The monkey's behavior, clinical samples, necropsy findings, and microscopic examinations were all normal (Adams et al. 1950).

Prendergast et al. (1967) studied the effects of repeated and continuous exposures to Trichloroethane in several animal species. The animals were exposed to 754 or 2059 mg/m^3 Trichloroethane by inhalation 8 h per day, 5 days per week, for 6 weeks. Additional groups of animals were exposed to 12,060 mg/m^3 Trichloroethane by inhalation continuously for 90 days. Each treatment group consisted of 15 rats, 15 guinea pigs, 3 rabbits, 2 dogs, and 3 monkeys. The control group consisted of 304 rats, 314 guinea pigs, 48 rabbits, 34 dogs, and 57 monkeys exposed only to room air.

Two rats and one rabbit in the 750 mg/m^3 continuous exposure group died on study. These deaths were not attributed to the Trichloroethane exposure. The surviving animals in the 750 mg/m^3 continuous exposure group had no signs of toxicity.

Continuous exposure to 2059 mg/m^3 Trichloroethane caused decreased body weight gain in dogs and rabbits, grey nodules on the lower left lobe of the left lung in one rat, and grape-like sacs containing clear fluid on the abdominal wall and adjacent organs of one rabbit. No other differences were observed between control and continuously exposed animals.

No animals died unexpectedly and no signs of toxicity were observed in the 12,060 mg/m^3 repeated-exposure group. Clinical chemistry, hematology, gross necropsy, and microscopic analysis revealed no remarkable observations (Prendergast et al. 1967).

Savolainen et al. (1977) exposed male Sprague-Dawley rats to 0 or 500 ppm Trichloroethane by inhalation, 6 h per day for 4 days (10 rats/treatment). On the 5th day, subsets of two rats each were exposed to the same concentration of the solvent by inhalation for 0, 2, 3, 4, 6 h. Exposure to Trichloroethane did not affect brain protein content, but the amount of RNA in brain tissue was lower in treated animals than in control animals on the 5th day. Activity of brain acid proteinase was slightly increased after the 6-h exposure on day 5. Ambulation frequency, preening time, rearing, defecation, and urination behaviors were no different in exposed and control animals.

Savolainen (1981) exposed male Wistar rats to 200 or 500 ppm Trichloroethane in an inhalation chamber 6 h per day for 4 days. One and 17 h after the end of the fourth exposure, the rats were evaluated for behavioral and neurochemical effects. The methods of evaluation were not described. Behavioral observations revealed no effects of the Trichloroethane exposure, but neurochemical analysis showed reduced DNA content of nervous tissue of exposed rats.

Subchronic Inhalation Toxicity

Torkelson et al. (1958) exposed various species to 500 ppm Trichloroethane by inhalation for 7 h per day, 5 days per week, for 6 months. The animals were 20 rats/sex, 8 guinea pigs/sex, 2 rabbits/sex, and 2 female monkeys. No signs of toxicity were found in clinical observations, weight gains, food consumption,

hematological parameters, gross necropsy, organ weights, or microscopic examinations in any species, other than as described below.

Female guinea pigs were exposed to 0, 1000, 2000 ppm Trichloroethane by inhalation for 0.05 to 3.0 h per day, 5 days per week, for 3 months. Increased liver weights were observed in animals exposed to 1000 ppm for 1.2 or 3.0 h per day or 2000 ppm for 0.5 h per day. Inflammation/irritation of the lungs and fatty liver were found in guinea pigs exposed to 1000 ppm for 3 h per day or 2000 ppm for 0.5 h per day.

The only sign of toxicity in four male rats exposed to 10,000 ppm Trichloroethane for 1 h per day, 5 days per week, for 3 months, was increased liver weight. Male rats exposed to 10,000 ppm Trichloroethane for 0.05 to 0.5 h per day, 5 days per week, for 3 months showed no signs of toxicity (Torkelson et al. 1958).

Rowe et al. (1963) studied the effects of repeated exposures to Trichloroethane in several animal species. Rats and rabbits were exposed to 500 or 1000 ppm Trichloroethane by inhalation 7 h per day, 5 days per week, for 6 months (8 to 10 rats/sex/exposure level and 3 rabbits/sex/exposure level).

There were no signs of toxicity observed in mortality, general appearance, behavior, hematological analysis, urinalysis, serum alkaline phosphatase, serum urea nitrogen, body weights, or relative and absolute organ weights. Microscopic analysis of the livers of rats in the 1000 ppm group revealed moderate diffuse cloudy swelling, occasional vacuolization, scattered foci of focal necrosis in the central portion of the lobules, and enlarged liver cells with hyperchromatic nucleus and prominent nucleolus. The kidneys of high-dose animals had a moderate degenerative change in the epithelial lining of the convoluted tubules. Rabbits in the high-dose group had similar findings as seen in the rats. No remarkable observations were noted in the rats or rabbits exposed to 500 ppm Trichloroethane.

Male and female dogs were exposed to 0, 500, or 1000 ppm Trichloroethane by inhalation 7 h per day, 5 days per week, for 6 months (1 dog/sex/exposure level). Appearance, behavior, mortality, growth, hematologic parameters, urinalysis, organ weights, blood urea nitrogen, alkaline phosphatase activity, and BSP retention were all similar between exposed and control animals. The female dog that was exposed to 1000 ppm Trichloroethane had enlarged liver cells with hyperchromatic nuclei. There was also an increased amount of connective tissue in the portal spaces. The male dog exposed to 1000 ppm Trichloroethane had only minimal changes in liver tissue, which were considered within normal limits. Tissues from dogs exposed to 500 ppm Trichloroethane were normal by microscopic examination.

Groups of nine male and eight female guinea pigs were scheduled to be exposed to 500 or 1000 ppm Trichloroethane by inhalation 7 h per day, 5 days per week, for 6 months with a pair-feeding design in which control animals were given amounts of food equal to the amounts consumed by exposed animals.

The decrease in food consumption was greater in the 1000 ppm group than in the 500 ppm group. Growth of treated animals was similar to growth in control animals given the same amount of food. However, food efficiency (gram of weight gained per grams of food consumed) was decreased in the 1000 ppm group.

Other observations during the exposures and in gross necropsy were similar between control and exposed animals. Microscopic changes in the liver and kidney of guinea pigs on the 1000 ppm group included moderate hydropic degenerative changes in the central areas of the lobule and foci of focal necrosis in the liver and degenerative changes in the epithelial lining of the convoluted tubules and round cell infiltration in the glomeruli and other interstitial tissues in the kidneys.

Guinea pigs in the 500 ppm group had slightly greater liver weights, but the authors considered this not to be toxicologically significant, because a similar increase was not seen at 1000 ppm (Rowe et al. 1963).

McNutt et al. (1975) exposed male CF-1 mice to 250 or 1000 ppm Trichloroethane by continuous inhalation for 14 weeks. Exposures occurred in large controlled environmental chambers. Control mice were exposed to ambient room air without added Trichloroethane. Subgroups of 10 animals per exposure level were killed weekly for necropsy and microscopic analysis during the 14-week exposure period. During the exposure period, the activity, food and water consumption, and general appearance of treated animals were similar to control animals.

Absolute liver weights were significantly increased ($p < .01$) in mice of the 1000 ppm group at weeks 2, 4, 7, 9, and 12 of exposure and in mice of the 250 ppm group at weeks 2 and 8. Relative liver weights were significantly increased ($p < .01$ to .05) in mice of the 1000 ppm group at every week of exposure and in mice of the 250 ppm group at weeks 2, 8, and 9. Liver triglyceride levels were elevated ($p < .01$ to .05) every week in the 1000 ppm group, except week 13, and at weeks 1, 3, 4, and 13 in the 250 ppm group.

Histologically, the livers of mice exposed to Trichloroethane had severe cytoplasmic alterations in the centrolobular hepatocytes in the 1000 ppm groups and mild to minimal effects in the 250 ppm group. The alterations included vesiculation of the rough endoplasmic reticulum, loss of attached polyribosomes, increased smooth endoplasmic reticulum, microbodies, and triglyceride droplets. Ballooned cisternae of the rough endoplasmic reticulum were also seen in some hepatocytes. Necrosis associated with acute inflammatory infiltrate and hypertrophy of Kupffer cells was also observed (McNutt et al. 1975).

Chronic Oral Toxicity

The National Cancer Institute (NCI 1976) conducted a 78-week oral gavage study of Trichloroethane in rats and mice.

In the original protocol, Osborne-Mendel rats were scheduled to be given 1500 or 3000 mg/kg day^{-1} Trichloroethane in corn oil, 5 days per week for 78 weeks (50 rats/sex/dose level). However, the study was terminated early because of signs of marked intoxication of the rats. The study was restarted using replacement animals. Osborne-Mendel rats were given 750 or

1500 mg/kg Trichloroethane in corn oil, 5 days per week for 78 weeks (50 rats/sex/dose level). A vehicle-control group consisted of 20 rats.

There was a decrease in body weight in both dosed groups during 1 year. Observations of urine staining began with a few dosed animals at week 10 and became more frequent in both dose groups. The occurrence of early mortality was significantly increased ($p < .04$) in both dose groups, compared to the control animals.

In the original protocol for the mouse study, B6C3F1 mice were to be given 2000 or 4000 mg/kg Trichloroethane in corn oil 5 days per week for 78 weeks (50 mice/sex/dose level). However, at week 10, it was apparent that the mice were tolerating the treatments very well, so the doses were increased to 2500 and 5000 mg/kg. At week 20, the doses were increased again to 3000 and 6000 mg/kg. A vehicle-control group consisted of 20 mice.

Reduced body weights and decreased survival rates occurred in both dose groups. The proportion of early female deaths in the dosed groups was significantly higher ($p = .002$), compared to that of control females (NCI 1976).

Chronic Inhalation Toxicity

Quast et al. (1988) studied the effects of chronic inhalation exposure to Trichloroethane in rats and mice. Fischer 344 rats and B6C3F1 mice were exposed to 0, 150, 500, or 1500 ppm Trichloroethane vapor in an inhalation chamber, 6 h per day, 5 days per week, for 2 years (5 animals/species/sex/dose level).

There was a decrease in body weights of the female rats exposed to 1500 ppm Trichloroethane for 2 years. Microscopic hepatic lesions were observed in male and female rats of the 1500 ppm group at 6, 12, and 18 months. These lesions were not considered to be toxicologically relevant, and they could not be seen at 24 months because of normal age-related changes in the rat livers. There were no significant observations in the 150 and 500 ppm exposure groups. The no observed adverse effect level for both rats and mice in this study was the highest dose tested, 1500 ppm Trichloroethane (Quast et al. 1988).

Neurobehavioral Toxicity

Krantz et al. (1959) investigated the value of Trichloroethane as an anesthetic in dogs and monkeys. In a study using 10 dogs, 0.34 ml/kg Trichloroethane (route unknown) induced anesthesia, whereas 0.60 mg/kg produced respiratory failure. In 10 rhesus monkeys, 0.28 ml/kg Trichloroethane was the anesthetic dose, and 0.59 ml/kg caused respiratory failure.

Larsby et al. (1978) studied the effect of intravenously injected Trichloroethane on vestibular function in rabbits. Rabbits were placed in a restraining box that could be darkened by closing the lid. A head holder secured the head in a steady position when the box was turned laterally. Subcutaneous electrodes were applied for electronystagmographic recordings. A 10% Trichloroethane solution was administered by continuous intravenous infusion. Duration of infusion, flow rate, and total dose administered were not reported. Arterial blood was collected frequently to monitor Trichloroethane concentrations. None of the rabbits exhibited any spontaneous or positional nystagmus before the infusion started. At blood concentrations below 75 ppm Trichloroethane, nystagmus was not observed. At 75 ppm and higher, 8 out of 10 rabbits had positional nystagmus (left beating in right lateral position and right beating in left lateral position). The positional nystagmus ended 5 to 10 min after the infusion stopped. At blood concentrations greater than 100 ppm, some of the rabbits had respiratory problems. No other remarkable toxic effects were noted.

Geller et al. (1982) trained young baboons on a match-to-sample discrimination task. Each animal was presented with a row of three translucent discs upon which stimuli of varying shapes could be projected. The baboons were trained to recognize a specific shape. When the disc with correct shape was pressed, the stimulus terminated and a banana-flavored food pellet would appear in a hopper below the discs. When an incorrect shape was pressed, the stimulus disappeared and no reward was given.

After the baboons were trained to recognize and respond to the correct stimulus shape, each was exposed to 700, 1400, 1800, and 2100 ppm Trichloroethane by inhalation for 4 h, with 1 week between exposures. The stimulus discrimination task was presented in the latter 2 h of the exposure period. Each animal's sequence of exposure concentrations was different. Three months later, the baboons were exposed to 1200 ppm Trichloroethane by inhalation continuously for 7 days. At the end of this extended exposure, the baboons were tested again on the stimulus discrimination task.

The baboons did not make more errors in the stimulus discrimination task during the 4-h exposure than during baseline (no exposure) trials. However, during the 1800 and 2100 ppm exposures, they made fewer attempts to press any stimulus and had longer response times when the correct stimulus was pressed. Similar effects were seen with the seven-day continuous exposure (Geller et al. 1982).

Mullin and Krivanek (1982) evaluated the effect of Trichloroethane exposure by inhalation on unconditioned reflex and condition avoidance tests in rats. Male Charles River-CD rats were exposed to 0, 1500, 3000, 6000, or 12,000 ppm Trichloroethane for 4 h (number of animals per group was not reported).

The unconditioned reflexes tested included motor activity, motor coordination, grip strength, righting reflex, pain (tail pinch), tactile and auditory startle reflexes, corneal reflex, and muscle tone. In the conditioned avoidance test, the rats were trained to avoid a mild electrical shock by pressing a level when presented with simultaneous visual and auditory stimuli (light and tone). Pressing the lever prevented the shock. The rats were tested for unconditioned reflexes and conditioned avoidance before exposure and at 0.5, 1, 2, and 4 h into the exposure period and again 18 h after exposure ended.

The rats began to fail the unconditioned reflex tests and the condition avoidance test with exposure to 3000 ppm Trichloroethane for 30 min. There was no effect on these parameters with 1500 ppm exposure (Mullin and Krivanek 1982).

Moser and Balster (1985) exposed male CD-1 mice to 2000 to 10,000 ppm Trichloroethane by inhalation for 10, 30, or 60 min (≥12 mice/exposure condition). At 1 min post exposure, the motor performance of the mice was evaluated with the inverted screen test. In this test, the mice were placed on a horizontal wire-mesh screen that was mounted on a horizontal rod. With the mouse on top of the screen, the screen was rotated 180° so that the mouse was inverted. Normally, mice will hang onto the screen and make their way to the edge and to the top side of the screen. The mice that fell off or were unable to climb to the top of the screen were considered affected. The inverted screen test was repeated every 15 min up to 4 h or until 11 mice per group had recovered.

At all three exposure concentrations tested, the number of mice to fail the inverted screen test increased from 10 to 30 min of exposure, with no additional increase at 60 min. The EC_{50} values of impaired motor performance were 7807, 5216, and 5674 ppm for the 10-, 30-, and 60-min exposures, respectively. Likewise, recovery time was 15 min after a 10- min exposure and 30 min for both the 30- and 60-min exposures (Moser and Balster 1985).

Kjellstrand et al. (1985) exposed NMRI mice to 890, 1300, 2000, or 4000 ppm Trichloroethane by inhalation for 1 h (17 mice/exposure level). During the hour of exposure, the motor activity of the mice was monitored by Doppler radar. Motor activity of the mice was increased during exposure to 2000 ppm Trichloroethane and decreased after the exposure ended. Mice exposed to 1300 ppm Trichloroethane had motor activity levels similar to control mice during exposure, but motor activity decreased after exposure. Mice in the 890 ppm group were unaffected by exposure. Results of 4000 ppm exposure were not described.

Moser and Balster (1986) trained male CD-1 mice to lever press under a fixed interval 60-s schedule for a reward (milk presentation). The mice were later exposed to 2000, 4000, 7000, or 10,000 ppm Trichloroethane by inhalation for 30 min and presented with the fixed interval lever test. Trichloroethane exposure decreased the fixed interval response rate with an EC_{50} of 7129 ppm (95% confidence limits: 6353 to 8147 ppm). Recovery to baseline response rate was rapid.

Nilsson (1986) studied the effects of Trichloroethane on cyclic guanosine monophosphate (cGMP) metabolism in mouse brain. Male mice were exposed to Trichloroethane either by inhalation (275 to 27,3000 mg/m^3 for 30 min to 4 h) or by i.p. injection (0.6, 1.2, 1.6, or 2.4 g/kg) and their behavior was monitored. At specific time points, the animals were killed by focused microwave radiation (1.5 kW for 1.6 s). The heads were immediately removed and chilled on ice. The cerebellum, brain stem, hippocampus, and cerebral cortex were removed. The cGMP content in each region of the brain was measured by radioimmunoassay.

Trichloroethane given by an i.p. injection of 0.6 to 2.4 g/kg reduced cGMP at different rates in the different brain areas. The vermis posterior and vermis anterior, including hemispheres, were the tissues most vulnerable to decreased cGMP levels, which occurred 20 min after injection. The cGMP levels in these tissues were restored to normal values 24 h after injection. Only the 2.4 g/kg dose decreased the cGMP levels in the hippocampus.

Inhalation of 275 or 375 mg/m^3 Trichloroethane did not affect cGMP levels in the mouse brains. The lowest effective exposure in decreasing cGMP was 550 mg/m^3 for 4 h, which decreased cGMP levels in the cerebellum. Levels of cGMP were maximally decreased in the cerebral cortex by 2730 mg/m^3 Trichloroethane. The cGMP in the brain stem was only decreased at the highest exposure, 27,3000 mg/m^3; cGMP in the hippocampus was not affected by any of the exposures tested.

Two hours after an i.p. injection of 2.4 g/kg Trichloroethane in male mice, guanylate cyclase activity was not affected in particulate or soluble fractions of the cerebellum, brain stem, and cerebral cortex. However, Trichloroethane inhibited sodium azide–stimulated activity of guanylate cyclase in the cerebellum. The Trichloroethane injection also increased the rate of hydrolysis of cGMP by phosphodiesterase in the cerebral cortex. The author proposed that Trichloroethane may reduce cGMP in the brain by inhibition of guanylate cyclase activity to produce cGMP and by stimulation of phosphodiesterase to remove cGMP (Nilsson 1986).

Rees et al. (1987) trained CD-1 mice to discriminate between intraperitoneal injections of 1 g/kg ethanol and saline in a two-lever operant conditioning task. The mice were later exposed to 125 to 14,000 ppm Trichloroethane by inhalation for 20 min and then challenged with the same two levers.

Exposure to Trichloroethane increased the ethanol-lever responding in a concentration-dependent manner. Clear increases in the percentage of ethanol-lever responses were observed at exposure concentrations of 1000 ppm to 10,000 ppm.

At the highest concentration tested (14,000 ppm), however, little ethanol-lever pressing was observed. A linear concentration-effect curve could not be fit to the entire concentration range tested. When the concentration range was limited to the ascending portion of the curve (1000 to 10,000 ppm), a median effective concentration (EC_{50}) of 850 ppm was obtained. The authors concluded that Trichloroethane has some behavioral and pharmacological effects in common with ethanol (Rees et al. 1987).

Evans and Balster (1993) found that mice repeatedly exposed to Trichloroethane can develop a physical dependence to the solvent. Male CFW mice were exposed to 0, 500, 1000, 2000, or 4000 ppm Trichloroethane by inhalation continuously for 4 days (10 mice/exposure level). Exposure was halted for 15 min each day to allow for daily weighing of the mice. At the end of the 4-day exposure period, mice were removed from the inhalation chamber and placed in home cages with ambient air.

The mice were observed for signs of withdrawal hourly for 12 h and every 12 to 14 h until complete recovery occurred. The severity and type of postexposure convulsions was scored to determine a withdrawal effect.

A few mice convulsed immediately after exposure ended. The maximum severity of withdrawal convulsions occurred at 2 to 4 h after removal from the chamber. In the 500 ppm and 1000 ppm groups, no more than 50% of the exposed mice exhibited convulsions at 2 to 4 h post exposure, and the number of convulsing mice was reduced thereafter. Eighty percent of mice in the 2000 ppm group were convulsing 2 to 5 h post exposure. Ninety percent of the mice in the 4000 ppm group were convulsing 2 to 8 h post exposure. Withdrawal was diminished in 80% of the mice by 24 h post exposure, but few mice in the 1000 and 4000 ppm groups continued to show withdrawal effects 2 days after exposure ended.

Based on the results of the above study, 2000 ppm was chosen as the exposure level to investigate the withdrawal effects of Trichloroethane. Additional mice were exposed to 0 or 2000 ppm Trichloroethane by inhalation continuously for 4 days. After this period, the mice were removed from the exposure chamber and returned to home cages with ambient air. Between 2 to 4 h post exposure (time of peak withdrawal), the exposed and control groups of mice were given one of the following drugs: 0.5, 1.0, or 2.0 g/kg ethanol; 30 mg/kg pentobarbital; 0.3 or 1.0 mg/kg midazolam; 30 mg/kg phenytoin; 3 or 5.6 mg/kg chlorpromazine; or 42, 48, or 56 mg/kg phenylenetetrazol (all drugs given intraperitoneally; 10 mice/Trichloroethane exposure condition/challenge drug). Additional groups of postexposure mice were returned to the inhalation chamber after 2 h of withdrawal and exposed to 2000 or 4000 ppm Trichloroethane or 1000 or 2000 ppm toluene for 30 or 60 min ($n = 10$ mice/exposure schedule).

The severity of withdrawal convulsions was significantly diminished ($p < .01$) by 30 or 60 min of exposure to 2000 or 4000 ppm Trichloroethane or 1000 or 2000 ppm toluene. Ethanol (1 or 2 g/kg), the sedative midazolam (0.3 or 1 mg/kg), and pentobarbital (30 mg/kg) were also effective in reducing the frequency and severity of withdrawal convulsions in mice. However, the anticonvulsant drugs chlorpromazine (3 mg/kg) and phenytoin (30 mg/kg) did not affect the withdrawal-induced convulsions. Phenylenetetrazol is a convulsion-producing drug and, when given to withdrawing mice at 48 or 56 mg/kg, increased the incidence and severity of convulsions and induced some deaths.

In considering these data, the authors proposed that prolonged exposure to Trichloroethane can produce physical dependence with withdrawal effects similar to those seen with other ethanol- and depressant-like drugs of abuse (Evans and Balster 1993).

Mattsson et al. (1993) exposed 14 Fischer 344 rats of each sex to 0, 200, 630, or 2000 ppm Trichloroethane by inhalation for 6 h per day, 5 days per week, for 13 weeks. Body weights and clinical observations were recorded before, weekly, during, and after the exposure period. The rats were given functional observational battery tests with forelimb and hindlimb grip strength tests before exposure, monthly during the treatment period, and after 13 weeks of exposure. Electrophysiological tests were performed about 3 days after the last exposure. Necropsy and microscopic examinations were focused on the brain.

There were no treatment-related effects in any of the behavioral or electrophysiological parameters tested, except for a reduced forelimb grip strength in the 2000 ppm exposure group for which there was no recognized toxicological significance. Necropsy and microscopic examinations of the brain were unremarkable. The authors found that Trichloroethane was not neurotoxic in this study (Mattsson et al. 1993).

Bowen and Balster (1996) exposed male CFW mice to Trichloroethane by inhalation using two exposure systems. One system used a static exposure chamber that recirculated vapor-laden air. The other used a dynamic exposure system that removed waste vapor with replacement of fresh vapor-laden air. The mice were exposed to 500, 1250, 2500, 5000, 7500, or 10,000 ppm Trichloroethane by inhalation using either the static or dynamic exposure system. An additional exposure concentration of 12,500 ppm was tested with the static system. Exposure durations were for 30 min. Both exposure chambers had been fitted with photocells to measure motor activity. Baseline motor activity rates were established prior to exposure to Trichloroethane.

In the static exposure chamber, Trichloroethane produced concentration-dependent increases in motor activity, with a minimum significant increase ($p < .001$) at 2500 ppm and a peak increase at 5000 ppm. The increase in motor activity at 7500 ppm was significant, but lower than the activity at 500 ppm. Mice exposed to 10,000 or 12,500 ppm Trichloroethane had activities similar to baseline.

The motor activity of mice exposed to Trichloroethane in the dynamic exposure chamber was significantly greater than baseline ($p < .001$) only at 1250 ppm. Exposures to 500, 2500, 5000, and 7500 ppm Trichloroethane produced no effect on motor activity in mice. The 10,000 ppm exposure produced a significant decrease in motor activity ($p < .05$), compared to baseline. Thus, in both exposure systems, Trichloroethane exposure on mouse motor activity was biphasic, with increases up to 5000 ppm and concentration-dependent decreases above 5000 ppm in the static system and a similar pattern with greater potency in the dynamic system (Bowen and Balster 1996).

Bowen et al. (1996) exposed adult male CFW mice to 0, 4000, 8000, 10,000, 13,300, or 18,000 ppm Trichloroethane by inhalation for 20 min ($n = 8$ mice/exposure level). During the last 2 min of exposure, the mice were scored on the following behavioral observations: posture, arousal, rearing, clonic movements, tonic movements, palpebral closure, gait, and gait abnormalities. Within 5 s of termination of the exposure period, the mice were removed from the chamber and scored for ease of removal, handling reactivity, piloerection, righting reflex, forelimb grip strength, inverted screen task, landing foot splay, approach response, click response, touch response, tail pinch response, and mobility. All postexposure observations were completed within 4 min after removal from the inhalation chamber.

During the last 2 min of the 20-min exposure to Trichloroethane, mice in the 8000 ppm group had increased arousal, whereas mice in the higher exposure groups showed a concentration-dependent decrease in arousal with animals becoming lethargic at the highest exposure of 18,000 ppm. Palpebral closure was the only autonomic effect observed during exposure and occurred only at the highest concentration. Gait was abnormal in the higher exposure levels during exposure and only at the highest treatment concentration after exposure.

After removal from the inhalation chamber, the exposed mice had concentration-dependent reductions in arousal, rearing, mobility, forelimb grip strength (13,300 and 18,000 ppm only), response to approach, response to a click sound, response to touch, and response to tail pinch (18,000 ppm only). The time for exposed mice to complete the inverted screen test was increased after exposure to 10,000 to 18,000 ppm, and the time taken to right themselves when placed on their backs was increased concentration-dependently in the 8000 to 18,000 ppm groups. The mice affected by exposure to Trichloroethane usually recovered within several minutes of removal from the inhalation chamber.

The authors concluded that acute inhalation exposure to Trichloroethane decreased central nervous system (CNS) activity, excitability, muscle tone, and sensorimotor activity. All of these behavioral effects were reversible. Additional groups of mice given intraperitoneal injections of 0.5 to 4.0 g/kg ethanol or exposed to 10,000 to 30,000 ppm ether by inhalation for 20 min had similar behavioral responses as those observed in the Trichloroethane exposure (Bowen et al. 1996).

Warren et al. (2000) compared blood and brain concentrations of Trichloroethane with relative effects on locomotor activity in mice. After a 30-min acclimation period in individual inhalation chambers with clean air, male Swiss-Webster mice were exposed to 500, 1000, 2000, 4000, 6000, 8000, 10,000, 12,000, or 14,000 ppm Trichloroethane by inhalation for 30 min (4 mice/exposure level). Each exposure chamber held one mouse and was divided by two sets of photocells. The movements of each mouse were quantified by the number of photocell breaks during the 30-min exposure period. Additional groups of mice were exposed to the same concentrations of Trichloroethane for 6, 12, 18, 24, or 30 min (4 mice/exposure concentration/exposure duration). At the end of each mouse's exposure period, the animal was killed by CO_2 asphyxiation, blood was collected from the vena cava, and the brains were collected within 2 min of death. The blood and brain samples were processed and analyzed by GC. The blood and brain concentrations of Trichloroethane were compared to the motor activities of mice receiving corresponding exposures to Trichloroethane.

Locomotor activity was not affected by 500 to 2000 ppm Trichloroethane. The mice exposed to 4000 to 8000 ppm Trichloroethane had increased motor activity that remained elevated for the duration of the exposure. Mice in the 10,000 to 14,000 ppm groups exhibited a biphasic response, with early increases in activity followed by decreased activity. Locomotor activity increased monophasically as solvent concentrations increased from about 50 to 150 μg/g brain tissue or 50 to 150 μg/ml blood. Between 150 and 250 μg/g brain (μg/ml blood), motor activity declined. At Trichloroethane concentrations above 250 μg/g brain (μg/ml blood), motor activity was reduced below baseline levels. Regression analysis showed very high correlations between motor activity and each of brain concentrations ($r = .95$) and blood concentrations ($r = .94$) (Warren et al. 2000).

Dermal Irritation

Torkelson et al. (1958) applied inhibited (containing 2.4% to 3.0% dioxane) or uninhibited Trichloroethane to the shaved abdominal skin of rabbits under occlusive bandages (doses and number of animals were not reported). After one 24-h application, slight reddening and scaling occurred. After 10 24-h applications over 12 days (15, 50, 100, 200, and 500 mg/kg day^{-1}), the severity of redness and scaling was only slightly increased. Healing was rapid after the exposure ceased. Slight reversible irritation was observed after the 24-h occluded dermal exposures to 500 mg/day Tricloroethane were repeated 5 days per week for 90 days. No signs of toxicity were observed in the 90-day dermal exposure.

Rowe et al. (1963) applied an unspecified amount of a mixture of 75% Trichloroethane and 25% tetrachloroethylene to the ears of rabbits nine times in 11 days without occlusion. Very slight erythema and exfoliation were observed. In another experiment, cotton pads wet with the mixture were applied to the shaved abdomens of rabbits. The pads were changed nine times in 11 days. Observations included slight to moderate erythema, slight edema, and slight exfoliation. When this procedure was repeated on abraded skin, moderate erythema, edema, and exfoliation were observed. A dermal dose as large as 30 mg/kg of the mixture produced some weight loss and superficial burning of the skin. In all studies described above, healing was complete within a week without scarring.

Kronevi et al. (1981) applied 1 ml of undiluted Trichloroethane to clipped skin on the backs of 17 anesthetized guinea pigs. The dosing site was inside a glass ring (internal diameter of 20 mm) with a circular exposure area of 3.1 cm^2. To prevent evaporation and inhalation of the test material, a glass cover was placed over the containment ring. At 15 min and 1, 4, and 16 h, the containment rings were removed, and skin samples from the dosed site and an adjacent nondosed site were cut away for biopsy (number of animals biopsied per time point was not reported). The samples were stained and examined microscopically.

No gross changes were seen in treated skin. Karyopyknosis was observed in the epidermis at all time points, most severe at 4 h but recovery was evident at 16 h. Karyolysis of the epidermis appeared at 4 h in some cells and in almost all cells at 16 h. Slight perinuclear edema of the epidermis was observed at all time points, somewhat more pronounced at 4 h. Spongiosis

of the epidermis was "marked" at 15 min and became "unrecognizable" at the other time points. Junctional separation was observed at all time points, and cellular infiltration of the upper part of the dermis was reported at 4 and 16 h. There were no remarkable observations in the untreated skin samples (Kronevi et al. 1981).

Bagley et al. (1996) compiled a data bank listing chemicals found to be irritants or corrosives to rabbit skin compiled for the European Centre for Ecotoxicology and Toxicology of Chemicals. The authors reported a primary irritation index of 5.22 on the skin of three rabbits exposed to undiluted Trichloroethane. The maximum possible score was 8. No further details were provided.

Ocular Irritation

Torkelson et al. (1958) applied a single dose of inhibited (containing 2.4% to 3.0% dioxane) or uninhibited Trichloroethane to the eyes of rabbits (volume delivered and number of animals were not reported). Signs of moderate pain and slight, transient conjunctival irritation were observed, with no corneal damage.

Krantz et al (1959) applied one drop of 5% Trichloroethane in corn oil to one eye of each of six rabbits. The treated eyes were observed for 12 h after exposure. Chemosis and hyperemia were observed.

Rowe et al. (1963) treated a rabbit eye with a mixture of 75% Trichloroethane and 25% tetrachloroethylene (volume not specified). The treatment caused immediate pain and slight conjunctival irritation which cleared within 48 h.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Lane et al. (1982) conducted a multigeneration reproduction study to examine teratogenic and dominant lethal effects of Trichloroethane. Male and female ICR Swiss mice (F_0 generation) received drinking water containing 0, 0.58, 1.75, or 5.83 mg/ml Trichloroethane (in 1% Emulphor to facilitate solubility) for 35 days (10 males and 30 females/exposure level). These concentrations were based on water consumption data to provide actual daily doses of 0, 100, 300, and 1000 mg/kg Trichloroethane, respectively.

F_0 mice were mated to produce F_{1A}, F_{1B}, and F_{1C} litters, with 2-week rest between weaning and subsequent mating. F_{1A} litters were examined and discarded. F_{1B} litters were culled to 30 females and 10 males per group, placed on appropriate Trichlorethane-drinking water solutions, and, at 14 weeks of age, mated with nonsiblings within the same treatment group to produce F_{2A} litters. After a 2-week postweaning rest, F_{1B} mice were mated again to produce F_{2B} litters. F_{1C} and F_{2B} litters were used in teratology and dominant lethal screening.

Parental and fetal analyses indicated no dose-dependent effects of Trichloroethane on fertility, gestation, viability, or lactation indices. Pup survival and growth were not affected by the solvent exposures. No significant dominant lethal mutations or teratogenic effects occurred in two generations of exposure to Trichloroethane in drinking water (Lane et al. 1982).

Research Triangle Institute (RTI) conducted two similar studies of the reproductive toxicity of Trichloroethane in drinking water given to rats before and during gestation, with a focus on effects on the development of the heart (RTI 1987a, 1987b).

In the first study (RTI 1987a), mature male and female COBS CD®(SD)BR outbred albino rats were given drinking water containing 3, 10, or 30 ppm Trichloroethane, with 0.05% Tween® 80 as an emulsifying agent. Two control groups received water either with no additives or with 0.05% Tween® 80 and 0.9 ppm 1,4,-dioxane, a stabilizing agent found in the Trichloroethane. There were 36 males and 36 females per treatment or control group.

The rats were exposed to the treated drinking water for 14 days prior to cohabitation, up to 13 days during the mating period, and mated females continued to be exposed throughout gestation, delivery, and until postnatal day 21.

The authors stated that Trichloroethane in water was difficult to formulate and unstable, which led to problems in calculating true levels of exposure to the test compound. Thus, it was necessary to calculate time-weighted averages of trichloroethane in the formulations. Based on the time-weighted averages, the estimated Trichloroethane consumption rates before mating were 267, 792, and 2388 μg/kg day^{-1} for males and 313, 994, and 2956 μg/kg day^{-1} for females in the 3, 10, and 30 ppm groups, respectively. The Trichloroethane consumption rates of pregnant dams during gestation were 348, 1162, and 3504 μg/kg day^{-1} and for 21 days after parturition were 605, 1987, and 5922 μg/kg day^{-1} in the three respective treatment groups.

There was a minimal dose-related decrease in water consumption and a slight dose-related increase in weight gain in males during the premating exposure period. A minimal dose-related decrease in water consumption was observed in females during the premating exposure period. There was no effect of Trichloroethane exposure on length of gestation.

There was a decrease in postnatal maternal weight gain in the 30 ppm group. A slight but significant increase in fetal mortality was observed in the 30 ppm exposure group. From postnatal days 1 to 21, there was no treatment-related effect on pup body weight, sex ratio, or pup survival. There was no evidence of cardiac or other malformations in pups examined on postnatal day 4 or 21 (RTI 1987a).

In the other reproductive study of Trichloroethane conducted by RTI (1987b), mature male and female COBS CD®(SD)BR outbred albino rats were given drinking water containing 3, 10, or 30 ppm Trichloroethane, with 0.05% Tween® 80 as an emulsifying agent. Two control groups received water either with no additives or with 0.05% Tween® 80 and 0.9 ppm 1,4-dioxane. There were 37 to 38 rats per sex per treatment or control group. The rats were exposed to the treated drinking water for 14 days prior to cohabitation, up to 13 days during the mating period, and mated females continued to be exposed throughout gestation.

Dams were killed for examination of the uterine contents on gestation day 20.

There was no significant adverse effect on body weight, food consumption, or water consumption during the premating exposure period and no evidence of maternal toxicity during gestation. There was no evidence of developmental toxicity or increase in malformations in fetuses at gestation day 20. No cardiac abnormalities in fetuses were observed (RTI 1987b).

George et al. (1989) gave male and female Sprague-Dawley rats drinking water that contained 0, 3, 10, or 30 ppm Trichloroethane (in 0.05% Tween®80 to facilitate solubility) for 14 days prior to cohabitation, up to 13 d during cohabitation (≥30 female rats/exposure level). Pregnant females continued to be exposed to the test formulations through gestation and lactation until postnatal day 21. The dams and offspring were killed and examined on postnatal day 21. A slight aversion to the 30 ppm formulation was exhibited by the parental rats. There were no effects of Trichloroethane exposure on the parental health, mating, implantation, fetal development, or postnatal development of rats in this study. No embryotoxic or teratogenic effects were observed.

Inhalation

Schwetz et al. (1975) studied the maternal and developmental toxicity of inhaled Trichloroethane in pregnant rats and mice. Treatment groups of 23 pregnant Sprague-Dawley rats and 13 pregnant Swiss-Webster mice were exposed to 875 ppm Trichloroethane by inhalation for 7 h per day on gestation days 6 through 15. Control groups of 30 pregnant rats and 30 pregnant mice were placed in the chamber on the same schedule but without Trichloroethane exposure. The mice were killed for maternal and fetal examinations on gestation day 18, and the rats were killed and examined on gestation day 21.

The maternal body weights of mice and rats were not affected by Trichloroethane exposure. The mean absolute liver weight of exposed rats was greater than that of control rats. Absolute liver weights in mice were not affected by exposure to the solvent. However, the mean relative liver weights were similar to those in control animals. Trichloroethane exposure had no effect on the average number of implantation sites per litter, litter size, the incidence of fetal resorptions, fetal sex ratios, or fetal body measurements in either species. The incidence of skeletal or visceral anomalies was similar between treated and control groups. Based on the results of this study, the authors concluded that Trichloroethane caused no maternal, embryonal, or fetal toxicity (Schwetz et al. 1975).

York et al. (1982) exposed female Long Evans rats to 2100 ppm Trichloroethane before and/or after mating. The animals were divided into four groups: exposure before and during pregnancy; exposure before pregnancy only, with sham exposure during pregnancy; exposure during pregnancy only, with sham exposure before pregnancy; and sham exposure before and during pregnancy (30 rats/ exposure schedule). Sham exposures consisted of placing the animals in the inhalation chamber on the same schedule but without Trichloroethane exposure. Premating exposures were for 6 h per day, 5 days per week, for 2 weeks. After the last exposure, the rats were mated with two females to one male. The presence of sperm in vaginal smears confirmed that mating had occurred. Gestational exposures occurred 6 h per day, 5 days per week, beginning the day mating was confirmed (gestation day 1) through gestation day 20.

On day 21 of gestation, half of the dams in each group were killed for necropsy and examination of the uteri and fetuses. The other half were allowed to deliver their litters. On postnatal day 4, the litters were randomly culled to four males and four females when possible. On postnatal day 20, the litters were randomly reduced again to two males and two females, which were kept alive for 12 months.

Female rats exposed to 2100 ppm Trichloroethane exhibited no signs of toxicity. Organ weights and blood chemistry parameters were not affected by Trichloroethane exposure. The two groups in which exposure to the solvent occurred prior to mating had significantly greater ($p < .05$) body weight gains during pregnancy than the two groups that received sham exposures before mating. The dams exposed to Trichloroethane both before and during gestation had fewer corpora lutea per litter ($p < .05$) than sham-exposed dams.

Mean female fetal body weights were not affected by solvent exposure. All other fetal survival parameters were similar between the exposure groups. No specific fetal skeletal or visceral defects occurred at greater frequency in any group, but animals exposed before and during gestation had a greater incidence ($p < .05$) of total skeletal anomalies and total soft tissue anomalies than the other groups.

There were no significant differences between the groups in litter weights from parturition to postnatal day 10 or in pup body weights from postnatal days 20 to 320. On postnatal day 21, pups from all four treatment groups performed similarly in an open field test in which photocell sensors quantified ambulatory activity in an unfamiliar environment.

On postnatal days 40 to 110, one male from each litter was housed in a running wheel, and the number of revolutions of the wheel was recorded on the last 12 days of this period. No significant differences were found between the four groups in number of wheel rotations.

At the end of the running wheel test, the male offspring in the group that was exposed to Trichloroethane only during gestation and the pre- and postmating sham groups were injected subcutaneously with saline and locked in the running wheel cage for 2 h. The next day, these rats were injected with 1 mg/kg amphetamine and put in the running wheel cage for 2 h. Four days later, these rats were dosed with 2 mg/kg amphetamine and put in the running wheel cage for 2 h. Exposure to Trichloroethane during pregnancy did not affect the wheel-running activity after either amphetamine injection. Gross necropsy and microscopic examinations in offspring 12 months after parturition

revealed no effects that could be attributed to prenatal exposure to Trichloroethane.

The authors concluded that prenatal exposure to 2100 ppm Trichloroethane did not produce any persistent maternal toxicity or teratogenicity and that the decreased fetal weights on gestation day 21 in the pre- and postmating exposure groups suggested only delayed development, as the delivered offspring in the same group had a normal growth rate (York et al. 1982).

Jones et al. (1996) studied the developmental effects of intermittent and continuous prenatal exposure to Trichloroethane in mice. In the continuous exposure study, pregnant CD-1 mice were exposed to 0 or 2000 ppm Trichloroethane by inhalation for 17 h per day on gestation days 12 to 17 (10 mice/exposure condition). Control animals (10 pregnant mice) were not treated. Mice in the control groups were pair-fed, according to food consumption values in the treated group. The dams were allowed to deliver their litters undisturbed.

The litters were culled to four males and four females when possible and fostered to surrogate mothers who had delivered with 24 h of the treated dams. The birth mothers were killed for examination of their uteri. One male and one female from each litter were assigned to one of four testing categories: physical development and motor activity, reflex development, muscle strength, or motor coordination.

No signs of maternal toxicity were apparent. Maternal weight gain during gestation, length of gestation, litter size, litter weight, and sex ratio were all similar between treated and control animals. The body weights of treated pups were reduced ($p < .05$), compared to that of sham-treated and untreated pups. The age of ear pinnae detachment, eye-opening, and incisor eruption was later in treated pups than in the two groups of control pups ($p < .01$).

Treated pups were slower or unable to perform the righting reflex on postnatal days 2 to 11 ($p < .01$), compared to control pups. The rooting reflex was not affected by Trichloroethane exposure. The treated pups had weaker forelimb strength ($p < .01$) on postnatal days 4 to 9, 11 to 12, and 14 than control pups. Treated pups took a longer time to correctly orient their body positions in the negative geotaxis and inverted screen tests ($p < .01$), compared to control pups. Motor activity was not affected by prenatal exposure to Trichloroethane.

There were no differences between sham exposed and untreated controls in any of the parameters tested. In the intermittent exposure study, pregnant CD-1 mice were exposed to 0 or 8000 ppm Trichloroethane by inhalation for three 1-h exposure periods per day on gestation days 12 to 17 (10 treated and 12 sham treated). The exposure periods were separated by 1-h recovery intervals. The behavior of the dams was monitored during and after each exposure. Upon parturition, the pups were fostered and subjected to behavioral tests identical to those described in the continuous exposure experiment above.

There were no clinical signs of maternal toxicity in the treated mice. The dams were nearly anesthetized and displayed ataxia, irregular gait, and clonic movements immediately after each exposure period. The dams were completely recovered by 1 h after each exposure. Maternal body weights during gestation, length of gestation, litter size, litter weight, and sex ratio were similar between the exposed and control groups. The age of ear pinnae detachment, eye-opening, and incisor eruption was later (by 1 day) in treated pups than in the control pups ($p < .01$ for each physical landmark).

Pups prenatally exposed to Trichloroethane performed more poorly or slowly in the righting reflex test, rooting reflex test, forearm grip strength test, and negative geotaxis test ($p < .01$ for each test). Performance on the inverted screen test was not affected by Trichloroethane exposure, and motor activity was similar between the treated and control groups. An additional test of learned passive avoidance in which mice were trained to avoid a mild 1-mA electric shock showed no significant difference in performance between treated and control pups.

The authors concluded that prenatal exposure to Trichloroethane can produce developmental toxicity in the offspring of exposed mice (Jones et al. 1996).

Coleman et al. (1999) exposed nine pregnant Sprague-Dawley CD rats to 7000 ppm Trichloroethane by inhalation for three 60-min intervals daily, each interval separated by a 60-min recovery period, on gestation days 13 through 19. Exposures took place in a 20.8-L sealed glass chamber. Ten sham-treated pregnant control animals were placed in an inhalation chamber on the same schedule without Trichloroethane exposure. A group of 19 untreated pregnant animals did not experience the inhalation chamber and were used as surrogate mothers after parturition.

Within 5 min of removal from the inhalation chamber, the Trichloroethane- and sham-exposed dams' behavior was evaluated with a functional observational battery. Upon parturition, the litters were counted and examined. The litters were culled to five male and five female pups when possible and fostered to untreated surrogate mothers who had given birth with 24 h of the treated dams. The treated dams were then killed and the uteri were examined for implantation sites to calculate fetal mortality. During the postnatal period, pups were evaluated by behavioral development tests, including righting reflex, negative geotaxis, vertical screen, grip strength, inverted screen, and motor activity. Physical development was evaluated by noting the age in days of the opening of eyes, detachment of ear pinnae, and eruption of incisors. On postnatal day 22, pups were killed, and their brains were weighed.

After Trichloroethane exposure on gestation days 13 to 19, salivation and lacrimation were increased with subsequent days of exposure. Ataxia, body dragging, and splaying of hindlimbs were observed in dams exposed to the solvent. Sham exposed animals had no salivation or lacrimation, and their gait was normal.

Dams exposed to Trichloroethane had reduced maternal weight gains, longer gestation periods, fewer live pups per litter, more resorptions per litter, a higher mortality index, and reduced

litter weights compared to sham-exposed dams ($p < .05$ for each parameter listed).

The offspring of Trichloroethane-exposed dams took longer to develop control of the orientation of their bodies, as measured by the negative geotaxis test ($p = .0177$) and inverted screen test ($p = .0105$). Sham-exposed pups had greater forelimb grip strength on postnatal days 8 to 20 ($p = .0078$) and were able to cling on to a vertical screen longer ($p = .0157$) than Trichloroethane-exposed pups. On postnatal day 21, sham-exposed pups were more active than pups exposed to Trichloroethane ($p = .0017$).

Pup weight gain was reduced in the Trichloroethane-exposed pups in the first 2 weeks of life ($p = .0268$). On postnatal day 22, the brain weights of sham-exposed pups were greater than the brain weights of solvent-exposed pups ($p = .0001$).

The authors stated that, based on the results of this study, Trichloroethane is a behavioral teratogen because it yields a pattern of maturational and behavioral deficiencies comparable to those caused by maternal consumption of ethanol (Coleman et al. 1999).

NTP (2000) gave male F344/N rats and B6C3F1 mice diets containing 5000, 10,000, 20,000, 40,000, or 80,000 ppm Trichloroethane administered in microcapsules in feed for 13 weeks (10 male animals/species/exposure level). Epididymal spematozoal concentrations of male rats and mice given 80,000 ppm Trichloroethane were significantly lower than those of control animals. Based on food consumption, 80,000 ppm Trichloroethane corresponded to intake rates of 4800 mg/kg day^{-1} in rats and 15,000 mg/kg day^{-1} in mice. The no observed effect level for reduced epididymal spermatozoa concentration was 40,000 ppm, or 2400 mg/kg day^{-1} in rats and 7370 mg/kg day^{-1} in mice.

GENOTOXICITY

Price et al. (1978) reported that exposure to 99 μM Trichloroethane induced transformations in an in vitro Fischer rat embryo cell system. A 9.9 μM treatment had no effect.

According to Nestmann et al. (1980), 2 mg/plate Trichloroethane was nonmutagenic in a standard Ames assay using *Salmonella typhimurium* strains TA1598, TA100, TA1535, TA1537, and TA1538 with and without S9 metabolic activation.

Gocke et al. (1981) reported that Trichloroethane was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 with and without S9 activation (concentrations tested were not reported). Trichloroethane was negative at 25 mM in the Basc test in *Drosophila* for sex-linked mutagenicity and was not active at 266 to 2000 mg/kg in an in vivo micronucleus test on mouse bone marrow.

According to Haworth et al. (1983), Trichloroethane at 33.0 to 10,000 μg/plate was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 with and without S9 activation. Cytotoxicity was noted at 10,000 μg/plate.

Arthur D. Little, Inc. (1983) reported the results of a BALB/c-3T3 cell transformation assay for Trichloroethane. Concentrations of 0, 4, 20, 100.0, and 250 μg/ml Trichloroethane were tested. All concentrations except the lowest (4 μg/ml) produced a significant increase ($p < .05$) in type III foci.

Shimada et al. (1985) reported that 2.5% Trichloroethane (with an unidentified nonmutagenic stabilizer) was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535. Cytotoxicity was apparent at 5.0% Trichloroethane. Results were similar with and without S9 metabolic activation.

In a rat hepatocyte DNA repair assay, up to 5.0% Trichloroethane was not mutagenic, but concentrations of 0.1% and higher were cytotoxic (Shimada et al. 1985).

Strobel and Grummt (1987) evaluated Trichloroethane in an Ames bacterial mutagenicity test. Salmonella strains TA98, TA100, TA97, and TA104 were treated withTrichloroethane (0.01 to 1.0 mg/plate) with or without S9 microsomal fraction. Trichloroethane at doses as low as 0.01 mg/plate appeared to be mutagenic in all four strains and more so in the presence of S9.

NTP (2000) reported a series of genotoxicity tests. At exposures up to 10,000 μg/plate, Trichloroethane was not mutagenic in the Ames bacterial reverse mutagenicity assay, using *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without S9 microsomal activation.

In the mouse lymphoma assay using L5178Y cells, up to 0.51 μg/ml Trichloroethane was negative in one test with and without S9 and was equivocal with S9 in another test. A concentration of 0.64 μg/ml was cytotoxic.

In a sister-chromatid exchange (SCE) assay using Chinese hamster ovary cells, the results for whether 60 to 500 μg/ml Trichloroethane induced SCE was equivocal in the presence or absence of S9. When the assay was repeated with 500 to 1000 μg/ml Trichloroethane without S9, the test material did not induce SCE.

Male mice exposed to up to 80,000 ppm Trichloroethane in drinking water for 13 weeks had a small but significant ($p = .015$) increase in the frequency of micronucleated normochromatic erythrocytes. The meaning of this small increase was considered equivocal by the authors. The peripheral blood micronucleus test in female mice was negative (NTP 2000).

CARCINOGENICITY

According to the International Agency for Research on Cancer (IARC 1999), there is inadequate evidence for the carcinogenicity of Trichloroethane in humans and in experimental animals.

Oral

NCI (1976) evaluated the carcinogenicity of Trichloroethane in rats and mice. Osborne-Mendel rats were given 750 or 1500 mg/kg Trichloroethane in corn oil by oral gavage 5 days per week for 78 weeks ($n = 50$ rats/sex/dose level). A vehicle-control group consisted of 20 rats.

In the original protocol for the mouse study, B6C3F1 mice were to be given 2000 or 4000 mg/kg Trichloroethane in corn oil

by oral gavage 5 days per week for 78 weeks (50 mice/sex/dose level). However, at week 10 it was apparent that the mice were tolerating the treatments very well, so the doses were increased to 2500 and 5000 mg/kg. At week 20, the doses were increased again to 3000 and 6000 mg/kg. A vehicle-control group consisted of 20 mice.

Because the incidence of various neoplasms was similar between dosed and control groups, and the neoplasms noted were known to occur in aging mice, the neoplasms observed were not attributed to the Trichloroethane treatment (NCI 1976).

Inhalation

Quast et al. (1988) studied the carcinogenicity of chronic inhalation exposure to Trichloroethane in rats and mice. Fischer 344 rats and B6C3F1 mice were exposed to 0, 150, 500, or 1500 ppm Trichloroethane vapor in an inhalation chamber, 6 h per day, 5 days per week for 2 years ($n = 5$ animals/species/sex/dose level). In this 2-year study, there were no indications of an oncogenic effect of Trichloroethane in rats or mice.

CLINICAL ASSESSMENT OF SAFETY

Trichloroethane in Human Tissue and Fluids

Barkley et al. (1980) collected samples of human breath, blood, and urine from residents of the Old Love Canal area of Niagara Falls, New York. The samples were analyzed by GC-MS for the presence of several chlorinated hydrocarbons. Trichloroethane was found in human breath from trace amounts to 2800 ppm ($n = 9$). Human blood samples contained 0.24 to 2.0 ng/ml and urine samples had 30 to 180 ng/L Trichloroethane ($n = 9$).

Antione et al. (1986) collected blood samples from 250 human subjects from the New Orleans, Louisiana, area. The blood samples were analyzed by GC-MS for the presence of volatile organic pollutants. The mean concentration of Trichloroethane in 250 blood samples was 1.0 ng/ml, and the range of concentrations was from below detection to 26 ng/ml. Five blood samples had a Trichloroethane concentration greater than two standard deviations above the mean.

Hajimiragha et al. (1986) measured the Trichloroethane content in whole blood from people who lived in several industrial cities in the Nordrhein-Westfalen region of Germany. Trichloroethane was detected in the blood of 23 out of 39 subjects who were not occupationally exposed to Trichloroethane. The range of Trichloroethane detected in these subjects' blood was <0.1 to 3.4 μg/L. Two out of nine automobile mechanics had detectable Trichloroethane in their blood (range 0.3 to 19.4 μg/L). Three out of 6 dry cleaner employees tested had detectable Trichloroethane in their blood (range 0.1 to 6.0 μg/L).

Ghittori et al. (1987) collected the urine of 60 workers who were occupationally exposed to Trichloroethane. The urine samples were analyzed by GC-MS, and the results were compared to the environmental concentrations of Trichloroethane to which the workers were routinely exposed. Although the specific urine and environmental concentrations were not reported, the correlation coefficient (r) of these two variable was 0.95, and the regression equation was $y = 0.45x + 12.6$ (where y = urinary concentration and x = environmental concentration in the breathing zone). The authors proposed a biological equivalent exposure limit (BEEL) of 805 μg/L.

Kroneld (1989) analyzed samples of human tissues from residents of the suburbs of Turku, Finland. The human tissue samples (kidney, lung, and muscle) were collected at hospitals and medical centers during surgery and pathological analyses. The samples were analyzed for the presence of chlorinated hydrocarbons by GC-MS. Human kidney, lung, and muscle samples contained 0.1 ± 0.08,0.1 ± 0.09, and0.4 ± 0.08 μg/kg Trichloroethane, respectively.

Clinical Tests

Torkelson et al. (1958) exposed human volunteers to Trichloroethane at 546 ppm for 90 min, 506 ppm for 450 min, 1000 ppm for 30 min, 920 ppm for 70 to 75 min, or 1900 ppm for 5 min (two to four subjects/exposure condition). Exposures occurred in a small room with vaporized Trichloroethane produced in a warm Petri dish in front of a circulating fan.

Subjects exposed to 546 ppm for 90 min had no complaints except for the odor of the Trichloroethane. Subjects exposed to 506 ppm for 450 min said that they had become unable to detect the odor of the chemical. There were no differences in blood pressure, pulse, respiration, reflexes, or equilibrium before and after exposure, and clinical tests indicated no changes in liver function. Subjects exposed to 1000 ppm for 30 min complained of the odor, but their equilibrium was not impaired. Of the four subjects exposed to 920 ppm for 70 to 75 min, two complained of the strong odor, one reported slight eye irritation, and three had a feeling of lightheadedness.

Electrocardiograms were normal throughout exposure. Coordination and equilibrium were impaired immediately after the exposure period, but recovery was complete within 5 to 10 min. Subjects exposed to 1900 ppm for 5 min complained of the strong odor and had obviously impaired equilibrium (Torkelson et al. 1958).

Dornette and Jones (1960) studied the use of Trichloroethane as a clinical anesthetic in 44 female and six male patients, aged 0 to 70 years, undergoing elective surgery. Trichloroethane (0.6% to 2.25%) was administered with 80% nitrous oxide and 20% oxygen. No attempt was made to perform surgery with Trichloroethane alone. The combination of Trichloroethane and nitrous oxide produced effective anesthesia and analgesia with rapid induction, rapid recovery, absence of respiratory depression, and absence of postoperative nausea and vomiting.

There was moderate depression of blood pressure during anesthesia, but blood pressure returned to normal when the concentration of Trichloroethane was reduced. Electrocardiograms revealed the following changes in cardiac rhythm during anesthesia: nodal rhythm (six patients); premature ventricular

contractions (five patients); and depressed S-T segments (two patients). One patient developed cardiac arrest while under anesthesia and died 2 weeks later from cerebral damage. Analysis of serum transaminases showed no evidence of hepatotoxicity.

The authors concluded that further studies were necessary before they would endorse the use of Trichloroethane as an anesthetic agent (Dornette and Jones 1960).

In the study by Stewart et al. (1961) reported earlier in "Absorption, Distribution, Metabolism and Excretion," clinical signs were noted and behavioral tests were performed before and after the exposure periods. The behavioral tests performed were the Romberg test (balancing on one foot with eyes closed and arms at one's side) and the heel-to-toe test.

Interval 1—500 ppm Trichloroethane for 78 min: Subjects complained of no subjective untoward effects. Postexposure performance was similar to corresponding preexposure data.

Interval 2—496 ppm Trichloroethane for 186 min: No subjective untoward effects were reported. Balance and coordination were not effected by Trichloroethane exposure, and the clinical data were normal.

Interval 3—955 ppm Tricloroethane for 73 min: Subjects required greater effort to perform the Romberg test after 10 min of exposure. No other subjective or clinical signs were reported.

Interval 4—910 ppm for 35 min: Subjects required greater effort to perform the Romberg test after 10 min of exposure. No other subjective or clinical signs were reported.

Interval 5—900 ppm for 20 min: Subjects required greater effort to perform the Romberg test after 10 min of exposure. One subject exposed to 900 ppm for 20 min had elevated urinary urobilinogen 7 days after exposure. No other subjective or clinical signs were reported.

Interval 6—0 to 2650 ppm over a period of 15 min: As the concentration increased from 0 to 1000 ppm, the subjects were increasingly aware of a slightly sweet, not unpleasant odor. Between 1000 and 1100 ppm, mild eye irritation was noted in six of the seven subjects. Between 1900 and 2000 ppm, six of the seven subjects complained of throat irritation. At 2600 ppm, one subject experienced light-headedness. At 2650 ppm Trichloroethane, two subjects were unable to stand and three subjects were very lightheaded but able to stand. Red blood cells were found in the urine of two subjects, but the authors stated that this finding was of uncertain significance because the inhibitor in the Trichloroethane was dioxane, a known renal toxin.

In considering the results of these six experiments, the authors supported 500 ppm as an appropriate threshold limit value for Trichloroethane (Stewart et al. 1961).

Rowe et al. (1963) exposed human subjects to 520 ppm Trichloroethane by inhalation for 1-, 4-, or 5-, 7-h exposures. The results of clinical tests on the exposed subjects were all within normal limits. One subject complained of a dryness in his throat during the exposure. The odor of the solvent was initially rated as strong but not objectionable at the first exposure. The odor became less perceptible as the exposure continued. After 5 h, the odor was rated as barely perceptible.

Stewart et al. (1969) studied human exposure to Trichloroethane vapor. Five volunteers were exposed to approximately 500 ppm Trichloroethane by inhalation for 6.5 to 7 h per day for 5 consecutive days. Complaints from the subjects included light-headedness, mild sleepiness, mild eye irritation, mild nose irritation, mild throat irritation, and mild headache. The odor of Trichloroethane was judged to be moderately strong during the first 5 min of exposure. Clinical and neurological assessments were normal in the exposed subjects, except for two subjects who had difficulty with the Romberg's test before and during exposure.

Salvini et al. (1971) exposed six male volunteers to 450 ppm Trichloroethane for two 4-h periods separated by a 1.5-h recovery interval. The solvent exposures were held 1 day before or 1 day after sham exposures on a similar schedule, in order to balance a sequence effect. Before and after the exposure, the subjects were tested with a tachistoscopic presentation task, Wechsler Memory Scale, a complex reaction time test, and a manual dexterity test. Exposure to Trichloroethane did not affect the subjects' performance on any of the psychophysiological tests in this study.

Gamberale and Hultengren (1973) exposed healthy male volunteers to Trichloroethane or regular air by inhalation and subjected them to tests of manual dexterity, perceptual speed, and reaction time. Six subjects were exposed to 250, 350, 450, and 550 ppm Trichloroethane in 4 30-min intervals, with a 5-min rest between the 350 and 450 ppm exposure. Seven days later, they repeated the procedures but with natural air instead of Trichloroethane. Six other subjects experienced the same exposure procedures but in reverse order (i.e., air exposure 7 days before Trichloroethane exposure).

The behavioral tests were performed during each exposure. Manual dexterity was tested by having the subjects guide 15 wire nuts individually along a 100 cm long wire labyrinth from one end of the wire to the other. Performance was based on time to complete the task with all 15 nuts. Perceptual speed was evaluated in two tests that asked subjects to identify identical numbers in lists of random numbers or to draw lines connecting in sequence randomly placed numbers on a page (as in connect-the-dots puzzles). Performance was rated on speed to complete each task. Subjects were allowed to practice all tasks before the experiment began, in order to prevent any effect of learning on performance.

Performance on all of the tests was slowed with exposure to Trichloroethane at concentrations of 350 ppm and higher. Performance was not significantly impaired at 250 ppm (Gamberale and Hultengren 1973).

Maroni et al. (1977) evaluated clinical, neurophysiological, and psychometric parameters in 22 female subjects who worked in a factory where Trichloroethane was the sole solvent used. The

air concentrations of Trichloroethane in the factory ranged from 110 to 990. The exposed subjects were compared to a matched reference group of seven unexposed women.

Clinical signs, maximal motor conduction velocity, conduction velocity of slow fibers, and psychometric data were similar between exposed and unexposed subjects. A slight but nonsignificant increase in the incidence of complaints of the neurotic type (headache, anxiety, psychic depression, digestive disorders, etc.) occurred in the exposed group. The exposed group had a significantly increased ($p < .05$) incidence of lower back pain.

The authors concluded that the results of this study showed no detectable changes in central and peripheral nervous functions in the exposed group, but cautioned that no definite conclusions on the neurotoxicity of Trichloroethane could be drawn from this study, because the sample was very small and the exposure time was moderate (Maroni et al. 1977).

Epidemiology

Kramer et al. (1978) conducted an epidemiology study of 151 matched pairs of employees of two adjacent textile plants. One of the plants used inhibited Trichloroethane as a general cleaning solvent, whereas the other did not. Employees of the plant that used Trichloroethane had experienced occupational exposure to various concentrations (up to 838 ppm) of the solvent for up to 6 years. Employees of the two plants were matched on sex, age, and smoking history. The cardiovascular and hepatic health of the exposed and control groups were compared. Hematology and clinical chemistry parameters were also examined. Statistical analyses revealed no clinically pertinent findings that were associated with exposure to Trichloroethane.

Case Reports

Hall and Hine (1966) reported two fatalities attributed to Trichloroethane poisoning. In the first case, the body of a 29-year-old male was found at home. Investigators determined that he had died of intentional inhalation of Trichloroethane from a cloth over his nose and mouth in an apparent act of suicide. The postmortem blood analysis revealed 13.0 mg % Trichloroethane but no other drugs or solvents.

The second case was of a 19-year-old female who had been observed inhaling Energine cleaning fluid for its intoxicating effects. She was later found dead with no apparent trauma. Postmortem blood analysis detected 72 mg % Trichloroethane and no other drugs or solvents. The death was attributed to accidental overdose as a result of solvent inhalation abuse (Hall and Hine 1966).

Stahl et al. (1969) reported six cases of fatal poisoning with Trichloroethane. Most of the victims had been using cleaning solvents containing Trichloroethane in poorly ventilated enclosed spaces. Analysis of the tissues of the victims found Trichloroethane concentrations of 0.15 to 12.0 mg/100 ml in the blood, 0.32 to 59.0 mg/100 g in brain tissue, and 0.49 mg to 22.0 mg/100 g in the liver.

Bass (1970) reported 29 sudden deaths attributed to solvent inhalation abuse of Trichloroethane between 1964 and 1969. The author described the probable cause of death in solvent abuse as severe cardiac arrhythmia.

Hatfield and Maykoski (1970) reported a case of a 27-year-old radiator and metal tank repairman who was found dead in a 450-gallon tank that he had been cleaning. Approximately 80 min after the body had been discovered, the air inside the tank was sampled and was found to contain 500 ppm Trichloroethane. The autopsy revealed no physical trauma. The victim's blood was found to contain 6 mg/100 ml Trichloroethane. No alcohol or other drugs were found in the blood, but there was a trace amount of carbon monoxide detected.

Stewart (1971) described four cases of Trichloroethane intoxication in adult men after working in conditions of high air concentrations of Trichloroethane. The primary effect was functional depression of the central nervous system. Symptoms began as dizziness and lassitude and progressed to unconsciousness, respiratory depression, and peripheral vascular collapse. Generally, recovery from the symptoms occurred by 16 to 17 h after the end of exposure to Trichloroethane.

Caplan et al. (1976) reported a case of a 40-year-old woman who died while cleaning a paint spill in an enclosed, poorly ventilated room. Her blood contained 1.0 to 1.5 mg/100 ml Trichloroethane at autopsy. The authors noted that this blood concentration of Trichloroethane is consistent with other Trichloroethane-related deaths reported in the literature.

Bonventre et al. (1977) reported the death of a case of a 20-year-old male who was employed as an oil burner repairman. He was found dead in a 4-foot-deep oil tank he that had been cleaning with a commercial degreasing solvent. In the postmortem analysis, Trichloroethane was detected in the victim's blood at 30 mg/dl and in the lung tissue at 24 mg/100 g. Ethanol and other drugs were not detected.

Gerace (1981) described a case of a 4-year-old boy who had spilled a 30-ml container of Trichloroethane from a craft kit under the covers of his bed. The child was well after 48 h and released. Six months later, a follow-up inquiry revealed no apparent long-term effects.

King et al. (1985) reported four cases of adolescents who died suddenly while inhaling typewriter correction fluid. Postmortem analyses revealed Trichloroethane in the blood (2.0 mg/L in one victim) and in lung tissue (concentrations not reported). Also present were trichloroethylene and, on one case, toluene. The deaths were considered accidents associated with solvent inhalation abuse.

Hodgson et al. (1989) reported four cases of patients with fatty liver disease whose occupations involved substantial exposure to Trichloroethane, although actual exposure levels were not determined.

Kelafant et al. (1993) reported that 28 workers who experienced long-term moderate- to high-exposures to Trichloroethane on the job suffered from mild encephalopathy, as measured by the Luria-Nebraska Neuropsychological Battery, Trail making

Test, Symbol Digit Modalities Test, and Personality Assessment Inventory. Ninety percent of the workers showed excessive somatic concerns and mild depressive symptoms. Postural control also seemed to be impaired in these subjects.

House et al. (1994) reported a case of a 44-year-old woman who complained of perioral tingling, a burning sensation on her tongue, and discomfort in her hands and feet. The woman had begun working as a hydraulic pump dismantler and parts cleaner approximately 18 months prior to experiencing her symptoms. The cleaner used in her daily duties was Trichloroethane, and no other chemical known to cause peripheral neuropathy were used. Two months after removal from the work environment, she noticed improvement in her lower limbs paresthesias, and cramping. All of her symptoms were resolved 6 months after removal from the work site.

SUMMARY

This safety assessment compiles relevant data on the safety of the use of Trichloroethane in cosmetic products. This ingredient is the 1,1,1-Trichloroethane isomer, which should be distinguished from the 1,1,2-trichloroethane isomer, which is not a cosmetic ingredient and is not reviewed in this safety assessment.

Trichloroethane is insoluble in water and soluble in acetone, benzene, carbon tetrachloride, methanol, and ether. It is not flammable and has an unpleasant odor at 1500 to 2000 ppm.

Trichloroethane is considered a Class I ozone-depleting substance by the EPA and its use is prohibited in the United States, unless considered essential. The FDA has determined that Trichloroethane in an aerosol cosmetic product is a nonessential use. EPA and FDA regulations address the use of Trichloroethane in food packaging, medical products, drugs, and drinking water.

Detection methods include gas chromatography, gas chromatography–mass spectrometry and gas-liquid chromatography. Trichloroethane has been found to be 98.76% pure with the remaining substances being 1,1-dichloroethane, 1,1,2-trichloroethane, and possibly perchloroethylene.

This function of Trichloroethane in cosmetic products is given as a solvent in the *International Cosmetic Ingredient Dictionary and Handbook*. Although this ingredient has been reported to FDA to be used in three cosmetic products, an industry survey found that it is not in current use in the cosmetic industry.

Trichloroethane was found in ambient air samples collected in a rural area of Washington state at 100 ± 15 ppt. In the Old Love Canal area of New York state, Trichloroethane was found in human breath (trace amounts to 2800 ppm), blood (0.24 to 2.0 ng/ml), and urine (30 to 180 ng/L); in air samples of the inside air of homes (up to 1200 ng/m^3); in outside air (5400 ng/m^3); and in drinking water (10 to 420 ng/L). Air samples near industrial chemical waste disposal sites in Louisiana and New Jersey contained Trichloroethane up to 8.8 and 120 μg/m^3, respectively.

Trichloroethane was found in the personal air, outdoor air, drinking water, and exhaled breath of people living in an industrial area of Bayonne-Elizabeth, New Jersey, and living in the rural agricultural community in North Dakota. In an area of small business industries in North Carolina, the chemical was found in personal air, outdoor air, and drinking water. Trichloroethane had at least a 5% greater detection frequency in the wells in urban areas than in nonurban areas in the United States.

Trichloroethane was found in the ambient air of the suburbs of Turku, Finland. The chemical was also found in the kidney, lung, and muscle tissue samples collected from patients in the suburbs of Turku, Finland. Trichloroethane was found in the exhaled breath and venous blood of factory workers from Singapore, who use Trichloroethane for degreasing and cleaning metals. In the southern North Sea, Trichloroethane was found at near background levels to 5.1 ng/L. Trichloroethane was found in the blood of people who lived in industrial cities but had no occupational exposure to the chemical in Germany.

In rats, Trichloroethane, whether inhaled or injected, is mostly expelled intact from the body through exhalation. A very small percentage is excreted in the urine. In humans, Trichloroethane is rapidly absorbed through the skin and eliminated in exhaled air and a very small percentage is excreted in urine. Inhaled Trichloroethane is eliminated in exhaled air.

Acute oral mean lethal concentration (LD_{50}) values are 12.3 g/kg in male rats; 10.3 g/kg in female rats; 11.24 g/kg in female mice; 5.66 g/kg in female rabbits; and 9.47 g/kg in male guinea pigs.

Subcutaneous injection produced an LD_{50} value of 120 mM/kg in mice. Intraperitoneal injection resulted in an LD_{50} value of 3.8 ml/kg (37 mM/kg) in mice and 3.1 ml/kg in dogs.

The LC_{50} of inhaled Trichloroethane in rats ranged from 15,000 ppm for 1 h to 10,500 ppm for 7 h in one study. Shorter durations of exposure, e.g., 10 min, resulted in an LC_{50} of 29,492 ppm.

Oral pretreatment of rats with ethanol increased Trichloroethane toxicity, as determined by bromosulfalein in the plasma. Oral pretreatment of rats with phenobarbitol did not affect Trichloroethane toxicity, as measured by AST activity. Oral pretreatment of mice with acetone or ethanol did not affect AST activity. Alloxan-induced diabetes in rats had no effect on Trichloroethane toxicity.

Inhalation of Trichloroethane reduced the hypnotic effects of phenobarbitol, but Trichloroethane, given via i.p. injection, increased the hypnotic effects of phenobarbitol. Trichloroethane, given via i.p. injection, increased the effects of epinephrine injections in dogs.

Trichloroethane inhalation by dogs resulted in cardiac arrhythmias in one study and decreased blood pressure and increased heart rate in another; a β-agonist prevented the increased heart rate. Inhalation by monkeys also increased heart rate and decreased blood pressure.

Liver toxicity was not seen in rats given 1650 mg/kg day^{-1} Trichloroethane by oral gavage for 7 days. Rats given

Trichloroethane in the diet at 4800 mg/kg day^{-1} for males and 5000 mg/kg day^{-1} for females produced minor, inconsistent pathology, but did result in decreased liver weights in males at the highest dose and non-neoplastic kidney lesions at doses above 600 mg/kg day^{-1}. Mice fed Trichloroethane at doses up to 15,000 mg/kg day^{-1} had reduced body weights, but no other effects.

Short-term inhalation toxicity studies in guinea pigs, rats, rabbits, and a monkey confirmed the acute inhalation toxicity study findings that the toxic effects of inhalation were a function of both concentration and time.

Continuous inhalation exposure of rabbits to 750 mg/m^3 for 90 days did not produce any signs of toxicity. Continuous exposure of rats, guinea pigs, rabbits, and monkeys to 500 ppm Trichloroethane for 6 months did not produce any signs of toxicity. Guinea pigs exposed to doses up to 2000 ppm for 30 min/day, 5 days/week, for 3 months, however, had increased liver weights. Other subchronic exposures confirmed acute and short-term exposure findings that the toxic effects of inhalation were a function of both concentration and time.

Chronic studies using rats dosed with 750 or 1500 mg/kg day^{-1} Trichloroethane in corn oil by oral gavage 5 days per week for 78 weeks resulted in reduced body weights and early mortality. Reduced body weights, decreased survival rates, and early mortality (in females) were found in mice dosed with 3000 or 6000 mg/kg day^{-1} (over the last 58 weeks; lower doses were administered for the first 20 weeks).

When placed into an inhalation chamber, mice exposed to prolonged periods of Trichloroethane had increased motor activity up to ~5000 ppm. Further increase of concentration of exposure results in less of an increase of motor activity until motor activity begins to fall below normal at 10,000 ppm.

Mice reportedly can develop a physical dependence on Trichloroethane when exposed continuously. Withdrawal convulsions occur at 2 to 4 h after termination of exposure. The use of Trichloroethane as an anesthetic in dogs and rhesus monkeys caused respiratory failure. Continuous intravenous infusion of Trichloroethane to rabbits caused positional nystagmus. Baboons made fewer attempts to press any stimulus and had longer response time after inhaling Trichloroethane continuously for 7 days. Rats began to fail unconditioned reflex tests and the condition avoidance test with exposure at 3000 ppm of 4 h. They also began to lose forelimb grip strength at 2000 ppm of exposure for 6 h/day for 5 days/week for 13 weeks.

Rabbits had slight reddening and scaling after 10 24-h applications to abdominal skin of Trichloroethane mixed with 2.4% to 3.0% dioxane. Slight to moderate erythema, slight edema, and slight exfoliation were observed when 75% Trichloroethane and 25% tetrachloroethylene were applied to rabbit ears for 11 days. Undiluted Trichloroethane applied to the clipped backs of guinea pigs produced no macroscopic changes, but damage was observed in the epidermis with histopathologic analysis. A primary irritation index of 5.22 (out of 8) was reported in rabbits.

Trichloroethane applied to the eyes of rabbits resulted in transient irritation and pain. There was no corneal damage.

There was no effect on gestation, pup survival, or growth in mice given Trichloroethane in drinking water at up to 5.83 mg/ml during mating and/or gestation. Rats exhibited no or minimal effects of ingestion of Trichloroethane up to 30 ppm in drinking water during mating and/or gestation.

There was no effect on gestation, pup survival, or growth in mice or rats inhaling 875 ppm Trichloroethane. However, prenatal exposure of rodents to Trichloroethane can produce developmental toxicity in the form of delayed development in the offspring.

This ingredient has been determined to be mutagenic in some Ames assays and not mutagenic in others. Trichloroethane-induced transformations in Fischer rat embryo cell system at 99 μM. Trichloroethane was not mutagenic using the mouse lymphoma assay up to 0.51 μg/ml wihout metabolic activation and was equivocal when tested with metabolic activation. Equivocal results were found in a sister-chromatid exchange assay using Chinese hamster ovarian (CHO) cells with and without metabolic activation.

Mice ingesting 80,000 ppm Trichloroethane in their drinking water had an increase in the frequency of micronucleated normochromatic erythrocytes. A peripheral blood micronucleus test in female mice did not produce an increased frequency of micronucleated cells.

Trichloroethane was not carcinogenic when administered 1500 mg/kg by oral gavage 5 days/week for 78 weeks using rats. The same result was found for mice administered 6000 mg/kg. When exposed to 1500 ppm Trichloroethane vapor for 6 h/day, 5 days/week, for 2 years, there were no indications of oncogenic effects in rats or mice.

The International Agency for Research on Cancer determined that there is inadequate evidence of human or animal carcinogenicity.

Humans inhaling Trichloroethane up to 500 ppm experienced lightheadedness and some loss of coordination. At 2650 ppm, subjects had difficulty standing and were very lightheaded. After exposure, subjects had difficulty with Romberg and other reaction and cognitive tests. There were complaints of sleepiness, eye irritation, nose irritation, throat irritation, and headache during exposure.

There are case reports that people have died from the inhalation of Trichloroethane by accident in poorly ventilated spaces and intentional overdose. People who have been exposed to Trichloroethane have reported dizziness, lassitude, unconsciousness, respiratory depression, peripheral vascular collapse, impaired postural control, mild encephalopathy, perioral tingling, burning on the tongue, and discomfort in the hands and feet.

DISCUSSION

At issue for this safety assessment is the safety of direct exposure to individuals as a result of exposure to cosmetic products

that may contain Trichloroethane. The Cosmetic Ingredient Review (CIR) Expert Panel emphasized that this assessment is only for 1,1,1-Trichloroethane and does not apply to its 1,1,2 isomer.

The CIR Expert Panel recognizes that Trichloroethane (1,1,1-Trichloroethane) has been declared a Class I ozone-depleting substance by the Environmental Protection Agency and its use is limited to essential products. The use of Trichloroethane in aerosol products or other pressurized dispensers, with the exception of "medical devices," is considered nonessential. Therefore, Trichloroethane may not be used in aerosol cosmetic products. It is the Panel's understanding that the use of Trichloroethane as a strictly nonaerosol cosmetic ingredient (i.e., as a solvent) does not fall under this prohibition. The CIR Expert Panel also noted that, for such use, however, Trichloroethane must be obtained through other channels than production or importation, such as through recycled Trichloroethane or stocks of Trichloroethane that existed prior to 1996.

The CIR Expert Panel also recognizes that, although this ingredient has been reportedly used in certain product categories, presumably as a solvent, a survey to determine use concentrations failed to uncover any reports of use. The survey results are consistent with the FDA determination that this ingredient is nonessential for cosmetic aerosol products.

Trichloroethane was not a reproductive or developmental toxicant or carcinogen in animal tests. Trichloroethane, at high concentrations, applied to human skin resulted in no ill effects. Inhalation of high levels of Trichloroethane, or exposures in confined spaces, is associated with adverse effects in humans, but neither of those conditions apply to the use in cosmetic products. Therefore, the available data do not suggest that direct human exposure to Trichloroethane from the use of cosmetic products would present any risk.

The CIR Expert Panel found the available data to be sufficient to support the safety of Trichloroethane as a solvent in cosmetic products.

CONCLUSION

The CIR Expert Panel concludes that based on the available safety data, Trichloroethane (1,1,1-Trichloroethane) presents no direct risk to the consumer from use in cosmetic products. However, the U.S. Environmental Protection Agency has banned its use as an ozone depleter from nonessential products and the U.S. Food and Drug Administration has determined that its use in aerosol cosmetic products is a nonessential use. Therefore, Trichloroethane may not be used in aerosol cosmetic products in the United States.

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