NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for 1,2,3-TRICHLOROPROPANE

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Prepared by

Integrated Laboratory Systems
Post Office Box 13501
Research Triangle Park, North Carolina 27709
NIEHS Contract No. N01-ES-25346

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NTP Report on Carcinogens Listing for 1,2,3-Trichloropropane

Carcinogenicity

1,2,3-Trichloropropane (TCP) is *reasonably anticipated to be a human carcinogen* based on evidence of malignant tumor formation at multiple sites in multiple species of experimental animals (NTP, 1993; Irwin et al., 1995).

TCP administered by gavage for 2 years induced tumors in male and female mice in the forestomach, liver, Harderian gland, uterus, and oral mucosa (females only), and in male and female rats in the forestomach, oral mucosa, pancreas (males only), kidney (males only), preputial gland, clitoral gland, Zymbal gland, and mammary gland (females only) (NTP, 1993; Irwin et al., 1995).

There are no adequate data available to evaluate the carcinogenicity of TCP in humans.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

TCP, when tested *in vitro,* induced gene mutations in bacteria, yeast, and mammalian cells; and sister chromatid exchanges, chromosomal aberrations, micronuclei, and morphological transformation in mammalian cells (Dean and Brooks, 1979; Sawin and Hass, 1982a,b; IARC, 1995; Doherty et al., 1996). TCP was active almost exclusively in the presence but not the absence of metabolic activation or when tested using metabolically competent cells. In *in vivo* rodent studies, TCP induced DNA damage, including DNA adducts in multiple tissues of rats and mice receiving the chemical by gavage or by intraperitoneal injection (IARC, 1995; La et al., 1995). TCP also induced proliferation in multiple tissues of rats and mice receiving the chemical by gavage or by inhalation (NTP, 1993; Irwin et al., 1995; Johannsen et al., 1988). TCP has been reported as negative for the induction of dominant lethal mutations in male rats (IARC, 1995). Several metabolites of TCP, including 1,3-dichloroacetone, induce genetic damage in a variety of short-term test systems (IARC, 1995). This metabolite is produced by human liver microsomes, although its rate of formation is less than in rats (Weber and Sipes, 1992).

No data are available that would suggest that the mechanisms thought to account for tumor induction by TCP in experimental animals would not also operate in humans.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

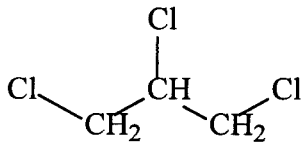
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 INTRODUCTION

1,2,3-Trichloropropane
[96-18-4]



1.1 Chemical Identification

1,2,3-Trichloropropane ($C_3H_5Cl_3$, mol. wt. = 147.43) is also called:

Propane, 1,2,3-trichloro- (8CI, 9CI)
Allyl trichloride
Glycerol trichlorohydrin
Glyceryl trichlorohydrin
NCI-C60220
Trichlorohydrin
Trichloropropane
1,2,3-TCP

1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless	Hawley (1981; cited by ATSDR, 1992)
Physical State	Liquid	Hawley (1981; cited by ATSDR, 1992)
Melting Point, °C	-14.7	Weast and Astle (1980)
Boiling Point, ° C	156.8	Weast and Astle (1980)
Density, g/cm^3 at 20 °C/4 °C	1.3889	Weast and Astle (1980)
Odor	Strong, acrid; trichloroethylene-like: "sweet" smelling	Ruth (1986); HSDB (1989); McNeill (1979), all cited by ATSDR (1992)
Solubility:		
Water at 20 °C, mg/L	1750	Riddeck et al. (1986; cited by ATSDR, 1992)
Organic Solvents	Soluble in: alcohol, ethyl ether, and chloroform	Weast and Astle (1980)
Partition Coefficients:		
Log octanol/water, log P	1.98	EPA (1988, cited by ATSDR, 1992)
Log K_{OC}	1.99 (estimated)	Lyman et al. (1982, cited by ATSDR, 1992)
Bioconcentration factor	9.2 (estimated)	Lyman et al. (1982, cited by ATSDR, 1992)
Vapor pressure at 25 °C, torr	3.1	McKay et al. (1982, cited by ATSDR, 1992)

1.3 Identification of Structural Analogues and Metabolites

Structural analogues and metabolites discussed in this report include the following:

1,3-Dichloro-2-propanol ($C_3H_6Cl_2O$, CASRN 96-23-1, MW = 128.99)
1,3-Dichloroacetone (DCA, $C_3H_4Cl_2O$, MW = 126.97)
2-Chloroacrolein (C_3H_3ClO, MW = 126.97)
2-(*S*-Glutathionyl)malonic acid (GMA)
2,3-Dichloro-1-propanol ($C_3H_6Cl_2O$, MW = 128.99)
N-Acetyl-(3-chloro-2-hydroxypropyl)-*L*-cysteine
1,2,-Dibromo-3-chloropropane
1,2-Dibromoethane

Physical-chemical properties were found for 1,3-dichloro-2-propanol and 1,3-dichloroacetone. Structures for some of these analogues may be found in Figure 6-1.

1,3-Dichloro-2-propanol

Property	Information	Reference
Solubility:		
Water	Soluble in water	Budavari et al. (1996)
Organic Solvents	Soluble in: alcohol, ethyl ether, and acetone	Weast and Astle (1980)

1,3-Dichloroacetone

Property	Information	Reference
Solubility:		
Water	Soluble in water	Weast and Astle (1980)
Organic Solvents	Soluble in: alcohol, ethyl ether, and acetone	Weast and Astle (1980)

1.4 Report Organization

The rest of this report is organized into six additional sections (2.0 Human Exposure, 3.0 Human Studies, 4.0 Mammalian Carcinogenicity, 5.0 Genotoxicity, 6.0 Other Relevant Data, and 7.0 References) and two appendixes. Appendix A describes the literature search in online databases, and Appendix B provides explanatory information for Figure 5-1.

2.0 HUMAN EXPOSURE

2.1 Use

In the past, 1,2,3-trichloropropane (1,2,3-TCP) has been used mainly as a solvent and extractive agent. As a solvent, it has commonly been used as a paint and varnish remover, a degreasing agent, and a cleaning and maintenance solvent. No current information is available to indicate that it is still used for these purposes. Currently, 1,2,3-TCP is used as a chemical intermediate in the production of polysulfone liquid polymers and dichloropropene, synthesis of hexafluoropropylene, and as a cross-linking agent in the synthesis of polysulfides. No data were available to indicate to what extent 1,2,3-TCP is currently used for these purposes (ATSDR, 1992). 1,2,3-TCP has been formulated with dichloropropenes in the manufacture of the soil

fumigant D-D (OHMTADS, 1972). According to the *Farm Chemicals Handbook '91* (Sine, 1991), this soil fumigant is no longer available in the United States.

2.2 Production

The *1994 Directory of Chemical Producers United States* identified two producers of 1,2,3-TCP (SRI, 1994). In 1985, two manufacturing facilities had a combined annual production greater than 10,000 pounds (NTP, 1993). In 1977, estimated production by four U.S. producers ranged from 21 to 110 million pounds, at least 10 million pounds of which was produced and used on-site (ATSDR, 1992; TSCAPP, 1983). More current production volumes could not be found.

1,2,3-TCP may also be produced in significant quantities as a byproduct of the production of other chlorinated compounds such as dichloropropene, propylene chlorohydrin (2-chloro-1-propanol or 2-chloro-2-propanol), propylene, dichlorohydrin (1,3-dichloro-2-propanol), glycerol (glycerin) (ATSDR, 1992), and epichlorohydrin (IFIS, 1985).

There were no data available on imports or exports of 1,2,3-TCP. Chem Sources (1996) identified 18 U.S. suppliers of 1,2,3-TCP as of February 1996.

2.3 Environmental Exposure

The primary route of potential human exposure to 1,2,3-TCP is inhalation of vapors. Other routes of exposure are ingestion and dermal contact.

2.3.1 Environmental Releases

1,2,3-TCP is not a naturally occurring chemical. Releases to the environment are likely to occur as a result of its manufacture, formulation, and use as a solvent and extractive agent, paint and varnish remover, degreasing agent, cleaning and maintenance reagent, and chemical intermediate. Releases may also occur as a result of the disposal of wastes from production of 1,2,3-TCP and disposal of products that contain the chemical, especially at hazardous waste sites that received 1,2,3-TCP-containing wastes (ATSDR, 1992) such as still bottoms of epichlorohydrin manufacture (RCRA waste number K017) (IFIS, 1985). 1,2,3-TCP has been detected in low concentrations in surface, drinking, and ground waters in various parts of the United States (ATSDR, 1992; NTP, 1993).

2.3.2 Environmental Occurrence

Members of the general population may be exposed to low levels of 1,2,3-TCP by ingestion of contaminated well water near a waste disposal site or agricultural lands treated with fumigants and nematocides that contain the compound as an impurity. Also, exposure may occur by inhalation of contaminated air near manufacturing facilities that use or produce the compound, and by inhalation near hazardous waste disposal facilities. 1,2,3-TCP has been detected at eight of the 1,177 U.S. EPA National Priorities List hazardous waste sites. It is uncertain how many NPL sites have been evaluated for this compound (ATSDR, 1992).

2.3.2.1 Ambient and Indoor Air

The accumulation of 1,2,3-TCP in shower and bathroom air during a typical shower was found to be small and was thought to be due to its low volatility (compared to other compounds studied). The low accumulation of 1,2,3-TCP in shower and bathroom air poses less serious

implications for institutional shower facilities (e.g., health clubs) than the more volatile VOCs (Little, 1992).

The U.S. Department of Health and Human Services (1992) was unable to estimate the U.S. atmospheric levels of 1,2,3-TCP, including background levels, because no data were found regarding the detection of this compound in ambient air in the United States (ATSDR, 1992).

2.3.2.2 Water

2.3.2.2.1 Groundwater

1,2,3-TCP was found in groundwater of 0.71% (8/1177) of the sites in the Contract Laboratory Program Statistical Database (CLPSD; includes data from both National Priorities List [NPL] and non-NPL sites) at a geometric mean concentration of 57.3 μg/L. It was not known how many of the 1177 sites had been actually evaluated for 1,2,3-TCP (CLPSD, 1989, cited by ATSDR, 1992). 1,2,3-TCP has been found in the drinking water of New Orleans, Louisiana, Cincinnati, Ohio, and Ames, Iowa (ATSDR, 1992, citing Keith, 1976; EPA, 1984; and EPA, 1987). 1,2,3-TCP was found in 39% of 941 U.S. groundwater samples recorded in EPA's STORET database at a median concentration from 0.69 μg/L, at an average concentration of 1.0 μg/L, and a range from trace (below unspecified detection limit) to 2.5 μg/L (EPA STORET, 1989, cited by ATSDR, 1992). It has been found in groundwater samples from California and Hawaii at concentrations ranging from 0.1 to 5.0 μg/L during small- and large-scale retrospective studies of farmlands possibly treated with fumigants and nematocides that contained 1,2,3-TCP as an impurity (Cohen et al., 1986, 1987, cited by ATSDR, 1992). Oki and Giambelluca (1987, cited by ATSDR, 1992) found 1,2,3-TCP in nine of nine wells in Oahu, Hawaii sampled in 1983 and 1984 at maximum concentrations ranging from 0.30 to 2.8 μg/L and several wells on Maui, Hawaii.

In Suffolk County, New York, 1,2,3-TCP has been detected in groundwater from 2 of 10 sites in an agricultural community at concentrations of 6 and 10 μg/L (Lykins and Baier, 1985, cited by ATSDR, 1992). 1,2,3-TCP was found in groundwater at the Ciba-Geigy Toms River Chemical Company plant, Ocean County, New Jersey (Barton, 1993).

2.3.2.2.2 Surface Water

In February, 1976, 1,2,3-TCP was qualitatively detected in 1 of 30 water samples taken from the Delaware, Schuylkill, and Lehigh Rivers (EPA, 1988). It was also qualitatively detected in water from Narragansett Bay, Rhode Island, sampled during the summers of 1979 and 1980, and the winters of 1980 and 1981; and in effluent from an advanced waste treatment plant in Lake Tahoe, California, in 1974 (Wakeham et al., 1983, and EPA, 1984; both cited by ATSDR, 1992). 1,2,3-TCP was found in grab sediment samples taken from the Grand Calumet River, Indiana, in October and November, 1988; March, May, October, and November, 1989; and May, 1990 (Hoke et al., 1992).

2.3.2.2.3 Sewage Sludge

Median and average concentrations of 1,2,3-TCP for sewage sludges from municipal sewage treatment plants in Michigan in 1980 were 0.352 and 1.07 mg/kg, respectively. On a dry weight basis, the range of 1,2,3-TCP concentration was from 0.00459 to 19.5 mg/kg (Jacobs and Zabik, 1983, cited by ATSDR, 1992).

2.3.2.3 Soil

Cohen et al. (1987, cited by ATSDR, 1992) found 1,2,3-TCP at levels ranging from 0.2 to 2 ppb in soil samples from Hawaii and California during small- and large-scale retrospective studies. The compound was found at least 10 feet down in the soil profiles in Hawaii. 1,2,3-TCP may have been present in these soil samples as a result of the use of dichloropropene (a soil fumigant and nematocide) (ATSDR, 1992). The detection of this compound in the groundwater of hazardous waste sites suggests that it is released to soil at these sites (ATSDR, 1992). 1,2,3-TCP was found in soil of 0.71% of the sites of the CLPSD (8/1177) at a geometric mean concentration of 204 µg/L (CLPSD, 1989, cited by ATSDR, 1992).

The primary removal processes of 1,2,3-TCP from soil are volatilization from near-surface soil and leaching to groundwater. 1,2,3-TCP may persist in groundwater for a relatively long period of time and it is thought that aerobic biodegradation is a slow process in natural waters and soil (ATSDR, 1992).

2.3.2.4 Other Environmental Media

1,2,3-TCP was qualitatively identified as a component of ethylene dichloride tar that had been disposed of by dumping into the sea; and the compound has also been found in the volatile products from the thermal oxidative degradation of the flame-retardant plasticizer tris(dichloropropyl) phosphate (Jensen et al., 1975; Christos et al., 1977; both cited by ATSDR, 1992).

2.3.3 Consumer Products

Inhalation and dermal exposures are possible during the use of consumer products such as certain paint removers. However, no data are available to indicate that the compound is currently used in consumer products or for any other purpose than as a chemical intermediate (ATSDR, 1992).

2.3.4 Occupational Exposure

The primary route of potential human exposure to 1,2,3-TCP is inhalation of vapors. Other routes of exposure are ingestion and dermal contact. Occupational exposures may result from procedures that require direct handling of the material: purification, formulation of products, sampling and quality control, packaging and storage, leakage of equipment, startup and shutdown procedures, maintenance, cleanup, spills, and other plant emergencies (NIOSH, 1981, cited by ATSDR, 1992).

The National Occupational Exposure Survey (1981-1983) indicated that 492 workers, including 9 women, were potentially exposed to 1,2,3-TCP (NIOSH, 1984). This estimate was derived from observations of the use of the actual compound (100% of total observations). The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 490 workers were potentially exposed to 1,2,3-TCP in the USA (NIOSH, 1976).

2.3.5 Populations With Potentially High Exposures

Persons whose drinking water is derived from 1,2,3-TCP-contaminated groundwater or surface water for a long period of time may be exposed to relatively high levels of this compound. The highest potential for human exposure to 1,2,3-TCP is thought to occur during

manufacture or use of 1,2,3-TCP or 1,2,3-TCP-containing products, such as paint- and varnish-removers and cleaners, especially when they are used in poorly ventilated areas such as in the cleaning of reactors. However, no current information indicates that 1,2,3-TCP is still used for these purposes (ATSDR, 1992).

Other populations with potentially high environmental exposure 1,2,3-TCP include those that can potentially be exposed to low levels of this compound via inhalation of contaminated air at or near both unidentified and identified 1,2,3-TCP-containing waste disposal sites and landfills. Children playing in and around these sites may also be exposed, by dermal absorption, to soil with this compound bound to it. However, little 1,2,3-TCP is expected to remain in surface soil since it would be expected to leach through the soil or volatilize (ATSDR, 1992).

2.4 Regulations

1,2,3-TCP is regulated by EPA under the Clean Air Act (CAA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and Safe Drinking Water Act (SDWA). Under CAA, the Synthetic Organic Chemicals Manufacturing Industry (SOCMI) is required to monitor equipment leaks of 1,2,3-TCP and to develop standards of performance. The SDWA requires community and non-community water systems to be monitored for 1,2,3-TCP. 1,2,3-TCP is listed as a hazardous constituent of waste under RCRA and is subject to minimum national detection criteria in groundwater from municipal solid waste sites. SW-846 analytical methods 8010, 8021, or 8260 with Practical Quantitation Limits (PQLs) of 10, 5, or 15 μg/L, respectively are suggested. Land disposal of liquid and nonliquid hazardous wastes containing $\geq$ 1000 mg/L or 1000 mg/kg (0.1%), respectively, are prohibited. A limit for 1,2,3-TCP in waste and non-wastewater has been set at 0.85 mg/L or 28 mg/kg, respectively. A Reference Air Concentration (RAC) for 1,2,3-TCP has been established at 0.1 μg/m^3. A reportable quantity (RQ) for 1,2,3-TCP has not been established under CERCLA.

OSHA requires employee access to exposure and medical records relating to exposure to 1,2,3-TCP. A Permissible Exposure Limit PEL of 300 mg/m^3 (50 ppm) has been established as an 8-hour Time Weighted Average (TWA). Although OSHA has not identified 1,2,3-TCP as an occupational carcinogen, NIOSH recommends that it should be treated as such and that maximum respiratory protection be used.

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 60.489. Effective 1/5/81. CAA: Standards of Performance for Equipment Leaks of Volatile Organic Compounds (VOCs) in the Synthetic Organic Chemical Manufacturing Industry (SOCMI).	
	40 CFR 141.40(e). Amended 57 FR 31845, 7/17/92. SDWA: Special monitoring for inorganic and organic chemicals.	Requires community water systems and non-transient, non-community water systems to monitor for selected chemicals.
	40 CFR 258, Appendix I. Amended 56 FR 51016, 10/9/91. Effective 10/9/93. RCRA: Constituents for detection monitoring of groundwater at municipal solid waste landfills, Subtitle D facilities. Class: Organic constituents.	Establishes minimum national criteria under RCRA for all municipal solid waste landfill (MSWLF) units and under CWA for municipal solid waste landfills that are used to dispose of sewage sludge.
	40 CFR 258, Appendix II. Effective 10/9/93. RCRA: List of hazardous inorganic and organic constituents for assessment monitoring of groundwater at municipal solid waste landfills (MSWLFs), Subtitle D facilities.	Groundwater at municipal solid waste sites to be monitored for 1,2,3-TCP using SW-846 methods 8010, 8021, or 8260 with Practical Quantitation Limits (PQLs) of 10, 5, or 15 μg/L, respectively. Suggested methods and PQLs are not part of the regulation.
	40 CFR 261, Promulgated 5/19/80, Amended through 8/31/93. Appendix III, Table 1 RCRA: Analytical methods for organic compounds contained in SW-846.	Specifies the appropriate SW-846 analytical method which will be used to determine whether a sample contains a given Appendix VIII toxic constituent. Method 8010 or 8240 is appropriate for 1,2,3-TCP.
	40 CFR 261, Promulgated 5/19/80, Amended through 8/31/93. Appendix VIII, RCRA: Hazardous constituents.	

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 264.90 et seq.; 40 CFR 264, Appendix IX, Promulgated 5/19/80, Amended through 5/24/93. RCRA: Releases from Solid Waste Management Units, Subtitle C facilities; Groundwater Monitoring List, Detection monitoring program, Compliance monitoring program.	Groundwater at hazardous waste sites to be monitored for 1,2,3-TCP using SW-846 method 8010 or 8240 with Practical Quantitation Limits PQLs) of 10 or 5 μg/L, respectively. Suggested methods and PQLs are not part of the regulation.
	40 CFR 266, Appendix IV. Amended 56 FR 32691, 7/17/91. Effective date 8/21/91. RCRA: Standards for the management of specific hazardous wastes and specific types of hazardous waste management facilities, boilers and industrial furnaces (BIF rule), including Reference Air Concentrations (RAC) for constituents listed in 40 CFR 261 Appendix VIII.	The RAC calculated for 1,2,3-TCP as indicated in the footnote to Appendix IV is 0.1 $\mu g/m^3$.
	40 CFR 268, Land Disposal Restrictions, Promulgated 5/28/86, Amended through 6/25/93; 40 CFR 268.32, Effective 7/8/87, Appendix III, RCRA: California list wastes prohibiting land disposal of specific halogenated compounds (HOCs).	California List prohibits land disposal of liquid and nonliquid hazardous wastes containing volatile HOCs in total concentrations $\geq$ 1000 mg/L or 1000 mg/kg, respectively.
	40 CFR 268.43. Amended 56 FR 3892, 1/31/91. RCRA: Hazardous constituent concentrations in Waste and Non-Wastewater.	Wastewater limit of 0.85 mg/L and non-wastewater limit of 28 mg/kg for 1,2,3-TCP.
	40 CFR 268.45, Table 2. Proposed rule published 57 FR 1026, 1/9/92. RCRA: Class CCO3, Halogenated aliphatic compounds. Land disposal restrictions (LDRs); Debris Treatment; Specific contaminants for each category.	Comments to the proposed rule were to have been submitted by February 24, 1992.

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 302, Appendix A, Amended 58 FR 35327, 6/30/93. Effective date 7/30/93. CERCLA: Reportable quantities for hazardous substances.	Notification of EPA is required if the reportable quantity of any of these substances is released into the environment. 1,2,3-TCP is listed in Appendix A with its CAS RN; however, it does not appear with a Reportable Quantity (RQ) in table 302.4.
OSHA	29 CFR 1910.20. Promulgated 7/1/88. OSH Act: Access to employee exposure and medical records.	Meets criteria for OSHA medical records rule by providing employees and their designated representatives a right of access to relevant exposure and medical records arising from exposure to any chemical listed in the latest Registry of Toxic Effects of Chemical Substances (RTECS).
	29 CFR 1910.1000 Subpart Z. Amended 7/27/93 (58 FR 40191). OSH Act: Limits for air contaminants.	Established PEL of 60 mg/m^3 (10 ppm), as an 8-hr TWA. Limit shall be achieved by any combination of engineering controls, work practices, and personal protective equipment.
	29 CFR 1915.1000, Table Z. Amended 58 FR 35514, 7/1/93. OSH Act, LHWCA: Toxic and hazardous substance air contaminant safety standards for shipyard employment.	PEL of 300 mg/m^3 (50 ppm) for 1,2,3-TCP. PEL is an 8-hr TWA.
	29 CFR 1917.1000, Table Z. Proposed rule published 57 FR 26558, 6/12/92. OSH Act, LHWCA: Toxic and hazardous substance air contaminant safety standards for long-shoring and marine terminals.	Written comments on the proposed standard must be postmarked on or before 9/25/92.
	29 CFR 1918.1000(a). Proposed rule published 57 FR 26575, 6/12/92. OSH Act, LHWCA: Toxic and hazardous substance air contaminant safety standards for long-shoring.	Written comments on the proposed standard must be postmarked on or before 9/25/92.

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
OSHA	29 CFR 1926.55, Table Z. Amended 58 FR 35089, 6/30/93. OSH Act, CWHSSA, CSA: Toxic and hazardous substance air contaminant safety standards for construction.	PEL of 300 mg/m^3 (50 ppm) for 1,2,3-TCP. PEL is an 8-hr TWA.
	29 CFR 1928.1000, Table Z. Proposed rule published 57 FR 26590, 6/12/92. Toxic and hazardous substance air contaminant safety standards for agriculture.	Written comments on the proposed standard had to be postmarked on or before 9/25/92.
	29 CFR 1990; 29 CFR 1990.103. Promulgated 45 FR 5282, 1/22/80. Establishes criteria and procedures for identification, classification, and regulation of potential occupational carcinogens.	NIOSH recommends that 1,2,3-TCP be treated as an occupational carcinogen even though OSHA has not identified it as such. To ensure maximum protection through the use of respiratory protection, only the most reliable and protective respirators are recommended. (There is no NIOSH criteria document for this compound.)

3.0 HUMAN STUDIES

No studies were found that evaluated the carcinogenicity of TCP in humans.

4.0 MAMMALIAN CARCINOGENICITY

Full experimental details for the studies described in this section are presented in Table 4-1.

Summary: There is "sufficient evidence" for the carcinogenicity of 1,2,3- trichloropropane in experimental animals (IARC, 1995). The incidences of tumors of the forestomach, oral mucosa (females only), liver, uterus, and Harderian gland were increased in B6C3F$_1$ mice treated with TCP by gavage for up to 2 years. The incidences of tumors of the forestomach, oral mucosa, pancreas (males only), kidneys (males only), preputial gland, clitoral gland, and mammary glands were increased in F344/N rats treated with TCP by gavage for up to 2 years. Doses for mice ranged from 6 to 60 mg/kg (41-407 μmol/kg) and doses for rats ranged from 3 to 30 mg/kg (20-203 μmol/kg) (NTP, 1993; Irwin et al., 1995).

4.1 Mice

In 6-week-old male and female B6C3F$_1$ mice administered TCP (6, 20, or 60 mg/kg [41, 136, or 407 μmol/kg]) by gavage 5 days per week for up to 2 years (NTP, 1993; Irwin et al., 1995), the incidence of squamous cell carcinoma of the oral mucosa was significantly increased in high-dose females only. In the forestomach, the incidences of squamous cell papilloma and squamous cell carcinoma were significantly increased in all TCP-treated mice. In the liver, the incidence of hepatocellular adenoma was significantly increased in mid-dose and high-dose males and in high-dose females. The incidence of hepatocellular carcinoma was only significantly increased in low-dose males. In the uterus, the incidence of carcinoma was significantly increased among all females of all TCP-treated groups. In the Harderian gland, the incidence of adenoma was significantly increased in mid-dose and high-dose males and in high-dose females. For details on tumor incidences, refer to Table 4-1.

4.2 Rats

In 6-week-old male and female F344/N rats administered TCP (3, 10, or 30 mg/kg [20, 68, or 203 μmol/kg]) by gavage 5 days per week for up to 2 years (NTP, 1993; Irwin et al., 1995), the incidences of squamous-cell papilloma and squamous-cell carcinoma of the oral mucosa were significantly increased in mid-dose and high-dose males and females. In the forestomach, the incidence of squamous-cell papilloma was significantly increased in all TCP-treated rats. The incidence of squamous-cell carcinoma of the forestomach was significantly increased in all TCP-treated males and in mid-dose and high-dose females. In the pancreas, the incidence of adenoma was significantly increased in all TCP-treated males, but not in females. In the kidneys, the incidence of adenoma was significantly increased in mid-dose and high-dose males, but not in females. In the preputial gland, the incidence of adenoma was significantly increased in high-dose males. In the clitoral gland, the incidence of adenoma was significantly increased in mid-dose and high-dose females. In the mammary glands, the incidence of adenocarcinoma was significantly increased in mid-dose and high-dose females. For details on tumor incidences, refer to Table 4-1.

Table 4-1. Mammalian Carcinogenicity Studies of 1,2,3-Trichloropropane

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Mice - *Oral Administration*							
6-wk-old $B6C3F_1$ mice	60M, 60F per dose	60M, 60F (corn oil alone)	TCP, > 99% pure	6, 20, or 60 mg/kg (41, 136, or 407 µmol/kg), 5 days/wk by gavage in corn oil	103 wk (LD males and male controls) 104 wk (LD females and female controls) 89 wk (MD males and females) 79 wk (HD males) 73 wk (HD females)	Mice were killed at the end of the treatment period or during an interim evaluation at ~ 15 months after the start of treatment. Complete histopathologic examinations were performed on all mice. The life table test and/or logistic regression tests were used to analyze tumor incidence. The life table test "regards neoplasms in animals dying prior to terminal kill as being the cause of death." The logistic regression test "regards these neoplasms as nonfatal." Survival of all TCP-treated mice was significantly lower than that of controls. **Oral Mucosa:** Positive (for squamous-cell carcinoma; HD females only) The incidence of squamous-cell carcinoma was significantly increased in HD females (5/60 vs. 0/60 controls; $p < 0.01$, life table test). Squamous-cell carcinoma was not detected in any males or females at the 15-month interim evaluation or in any males at the end 2 years. **Forestomach:** Positive (for squamous-cell papilloma and squamous-cell carcinoma at all doses) The incidence of squamous-cell papilloma was significantly increased in all TCP-treated mice (males: 35/59 LD, 25/60 MD, 35/60 HD vs. 3/60 controls [$p < 0.01$, logistic regression test]; females: 28/60 LD, 27/60 MD, 33/60 HD vs. 0/60 controls [$p < 0.01$, logistic regression test]). At the 15-month interim evaluation, squamous-cell papilloma was detected in 7/8, 3/6, and 2/4 LD, MD, and HD males, respectively (vs. 0/8 controls, p-value not given) and in 5/10, 9/9, and 4/5 LD, MD, and HD females, respectively (vs. 0/10 controls, p-value not given). The incidence of squamous-cell carcinoma was significantly increased in all TCP-treated mice (males: 41/59 LD, 54/60 MD, 55/60 HD vs. 0/60 controls [$p < 0.01$, life table test]; females: 47/60 LD, 55/60 MD, 51/60 HD vs. 0/60 controls [$p < 0.01$, life table test]). At the 15-month interim evaluation, squamous-cell carcinoma was detected in 1/8, 4/6, and 4/4 LD, MD, and HD males, respectively (vs. 0/8 controls, p-value not given) and in 1/10, 6/9, and 2/5 LD, MD, and HD females, respectively (vs. 0/10 controls, p-value not given).	NTP (1993) Irwin et al. (1995)

Table 4-1. Mammalian Carcinogenicity Studies of 1,2,3-Trichloropropane (Continued)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Mice - *Oral Administration* (Continued)							
6-wk-old B6C3F$_1$ mice	60M, 60F per dose	60M, 60F (corn oil alone)	TCP, > 99% pure	6, 20, or 60 mg/kg (41, 136, or 407 µmol/kg), 5 days/wk by gavage in corn oil	103 wk (LD males and male controls) 104 wk (LD females and female controls) 89 wk (MD males and females) 79 wk (HD males) 73 wk (HD females)	**Liver:** Positive (for hepatocellular adenoma; MD and HD males and HD females only) The incidence of hepatocellular adenoma was significantly increased in MD and HD males and in HD females (males: 21/60 MD [$p < 0.05$, logistic regression test], 31/60 HD [$p < 0.01$, logistic regression test] vs. 12/60 controls; females: 36/60 HD [$p < 0.01$, logistic regression test] vs. 7/60 controls). At the 15-month interim evaluation, hepatocellular adenoma was detected in 0/8, 0/6, and 2/4 LD, MD, and HD males, respectively (vs. 1/8 controls, p-value not given) and in 0/10, 1/9, and 5/5 LD, MD, and HD females, respectively (vs. 1/10 controls, p-value not given). The incidence of hepatocellular carcinoma was only significantly increased in LD males (11/59 vs. 4/60 controls [$p < 0.05$, logistic regression test]). **Uterus:** Positive (for carcinoma) The incidence of uterine carcinoma was significantly increased in all TCP-treated females (4/60 LD, 3/60 MD, 8/59 HD vs. 0/60 controls; $p < 0.01$, life table test). At the 15-month interim evaluation, uterine carcinoma was only detected in 2/5 HD females (significance not specified). **Harderian Gland:** Positive (for adenoma; MD and HD males and HD females only) The incidence of Harderian gland adenoma was significantly increased in MD and HD males and in HD females (males: 10/60 MD, 11/60 HD vs. 1/60 controls [$p < 0.01$, logistic regression test]; females: 10/60 HD vs. 3/60 controls [$p < 0.05$, logistic regression test]. Harderian gland adenomas were not detected in any TCP-treated mice at the 15-month interim evaluation. Rats were killed at the end of the treatment period or during an interim evaluation at ~ 15 months after the start of treatment. Complete histopathologic examinations were performed on all rats. The life table test and/or logistic regression tests were used to analyze tumor incidence. Survival of MD and HD rats was significantly lower than that of controls.	*NTP (1993) Irwin et al. (1995)

Table 4-1. Mammalian Carcinogenicity Studies of 1,2,3-Trichloropropane (Continued)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Rats - *Oral Administration*							
6-wk-old F344/N rats	60M, 60F per dose	60M, 60F (corn oil alone)	TCP, > 99% pure	3, 10, or 30 mg/kg (20, 68, or 203 μmol/kg) 5 days/wk by gavage in corn oil	103 wk (LD and MD males and male controls) 104 wk (LD and MD females and female controls) 77 wk (HD males) 67 wk (HD females)	**Oral Mucosa:** Positive (for squamous-cell papilloma and squamous-cell carcinoma; MD and HD rats only) The incidence of squamous-cell papilloma was significantly increased in MD and HD TCP-treated rats (males: 10/59 MD, 22/60 HD vs. 0/60 controls [$p < 0.01$, logistic regression test]; females: 10/60 MD, 21/60 HD vs. 1/60 controls [$p < 0.01$, logistic regression test). At the 15-month interim evaluation, squamous-cell papilloma was detected in 1/10 MD and 3/8 HD males and in 3/8 HD females (vs. 0/10 male and 0/10 female controls; p-values not given). The incidence of squamous-cell carcinoma was significantly increased in MD and HD TCP-treated rats (males: 11/59 MD, 25/60 HD vs. 1/60 controls [$p < 0.01$, life table test]; females: 21/60 MD, 23/60 HD vs. 0/60 controls [$p < 0.01$, life table test). At the 15-month interim evaluation, squamous-cell carcinoma was only detected in 2/8 HD females (significance not specified). **Forestomach:** Positive (for squamous-cell papilloma and squamous-cell carcinoma at all doses) The incidence of squamous-cell papilloma was significantly increased in all TCP-treated rats (males: 31/60 LD, 36/59 MD, 46/60 HD vs. 0/60 controls [$p < 0.01$, logistic regression test]; females: 14/59 LD, 37/59 MD, 24/60 HD vs. 0/60 controls [$p < 0.01$, logistic regression test]). At the 15-month interim evaluation, squamous-cell papilloma was detected in 2/10, 3/10, and 8/8 LD, MD, and HD males, respectively, (vs. 0/10 controls; p-value not given) and in 1/10, 5/8, and 7/8 LD, MD, and HD females, respectively (vs. 0/10 controls; p-value not given). The incidence of squamous-cell carcinoma was significantly increased in all TCP-treated males and in MD and HD females (males: 9/60 LD, 28/59 MD, 14/60 HD vs. 0/60 controls [$p < 0.01$, life table test]; females: 9/59 MD, 6/60 HD vs. 0/60 controls [$p < 0.01$, life table test]). At the 15-month interim evaluation, squamous-cell carcinoma was detected in 0/10, 1/10, and 1/8 LD, MD, and HD males, respectively (vs. 0/10 controls; p-value not given), and in 0/10, 0/8, and 2/8 LD, MD, and HD females, respectively (vs. 0/10 controls; p-value not given). **Pancreas:** Positive (for adenoma; males at all doses only) The incidence of adenoma was significantly increased in all TCP-treated males (21/60 LD, 37/59 MD, 31/60 HD vs. 5/60 controls [$p < 0.01$, logistic regression test]). The incidence of adenocarcinoma was not significantly increased in males. In females, adenoma was only detected in the MD group (2/60; not significant). At the 15-month interim evaluation, adenoma was detected in only 1/10 MD and 2/8 HD males (p-values not given). Adenoma was not detected in any females at the 15-month interim evaluation.	*NTP (1993) Irwin et al. (1995)

Table 4-1. Mammalian Carcinogenicity Studies of 1,2,3-Trichloropropane (Continued)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Rats - *Oral Administration* (Continued)							
6-wk-old F344/N rats	60M, 60F per dose	60M, 60F (corn oil alone)	TCP, > 99% pure	3, 10, or 30 mg/kg (20, 68, or 203 µmol/kg) 5 days/wk by gavage in corn oil	103 wk (LD and MD males and male controls) 104 wk (LD and MD females and female controls) 77 wk (HD males) 67 wk (HD females)	**Kidneys:** Positive (for adenoma; MD and HD males only) The incidence of adenoma was significantly increased in MD and HD males (20/59 MD, 26/60 HD vs. 0/60 controls [$p < 0.01$, logistic regression test]). At the 15-month interim evaluation, adenoma was only detected in HD males (5/8; p-value not given). In females, the incidence of adenoma was not listed, but the incidence of adenocarcinoma in females was not significant (1/59 HD females; not significant). The incidence of adenocarcinoma in males was not listed. **Preputial Gland:** Positive (for adenoma; HD males only) The incidence of adenoma was significantly increased in HD males (11/58 vs. 5/59 controls [$p < 0.05$, logistic regression test]). At the 15-month interim evaluation, adenoma was only detected in 1/10 MD males (p-value not given). **Clitoral Gland:** Positive (for adenoma; MD and HD females only) The incidence of adenoma was significantly increased in MD and HD females (14/58 MD [$p < 0.01$, logistic regression test], 12/59 HD [$p < 0.05$, logistic regression test] vs. 5/56 controls). At the 15-month interim evaluation, adenoma was detected in 1/10, 1/8, and 2/8 LD, MD, and HD females, respectively (vs. 0/10 controls; p-value not given). **Mammary Glands:** Positive (for adenocarcinoma; MD and HD females only) The incidence of adenocarcinoma was significantly increased in MD and HD females (12/60 MD, 22/60 HD vs. 1/60 controls [$p < 0.01$, life table test]). At the 15-month interim evaluation, adenocarcinoma was only detected in 1/8 HD females (p-value not given).	* NTP (1993) Irwin et al. (1995)

5.0 GENOTOXICITY

Studies of the genotoxic effects of TCP are summarized in Table 5-1.

Summary: TCP was found to be genotoxic in a number of prokaryotic and mammalian *in vitro* test systems in the presence of metabolic activation or in metabolically competent cells [see Genetic Activity Profile, Figure 5-1 (data limited to IARC, 1995). TCP was found to induce gene mutations in repair-deficient *Escherichia coli* tester strain WP2*uvr*A, *Salmonella typhimurium*, and mouse lymphoma L5178Y cells. Mitotic gene conversions were observed in *Saccharomyces cerevisiae*; sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) and lung V79 cells; micronuclei in human lymphoblastoid cells; and chromosomal aberrations in CHO cells. It was also positive for morphological transformation in Syrian hamster embryo cells, DNA damage and covalent DNA binding in rat hepatocytes in vivo, and DNA adducts in several tissues of mice and rats. It was negative for the induction of SOS repair in *E. coli*, chromosomal aberrations in rat liver RL_4 cells, and unscheduled DNA synthesis (UDS) in rat hepatocytes (both *in vitro* and *in vivo*), and DNA-protein cross-links and dominant lethal mutations in rats.

Unless otherwise noted, rat liver S9 was the source of metabolic activation *in vitro*. In addition, for simplicity, multiple citations in IARC for the same genetic toxicity assay were discussed as a group rather than individually.

5.1 Noneukaryotic Systems

5.1.1 DNA Damage

As reviewed by IARC (1995), von der Hude et al. (1988) found that TCP did not induce SOS repair as measured by the chromo test in *E. coli* strain PQ37 (dose levels were not provided) either in the presence or absence of metabolic activation.

5.1.2 Gene Mutations

TCP, in the presence of metabolic activation, induced mutations in repair deficient *E. coli* tester strain WP2*uvr*A [LED = 2000 µg (14 µmol)/plate]. In the same strain in the absence of metabolic activation, or in the repair proficient strain WP2 in either the presence or absence of metabolic activation, TCP was negative for mutation induction [HID = 2000 µg (14 µmol)/plate] (Dean and Brooks, 1979). In the Salmonella reverse mutation assay, Dean and Brooks (1979) concluded that TCP was weakly positive (2.7- to 4.6-fold) in *S. typhimurium* strain TA1535 without metabolic activation [LED = 200 µg (1.4 µmol)/plate] and strongly positive (16.6- to 35.5-fold) with metabolic activation [LED = 20 µg (0.14 µmol)/plate]. When tested at doses ranging from 0.2 (0.0014 µmol) to 2000 µg (14 µmol)/plate, it was also positive in strains TA 98, TA1537, TA100, and TA1535 with metabolic activation only [LEDs not provided; HID = 2000 µg (14 µmol)/plate].

IARC (1995) reported on 5 microbial mutagenicity studies with TCP. It was mutagenic in *S. typhimurium* strains TA100, TA97, TA98, TA1535, TA1537, and TA1538 only in the presence of metabolic activation [LED = 5.5 µg/plate (0.04 µmol/plate)].

Ratplan and Plaumann (1988; cited by IARC, 1995) reported that it was not mutagenic in *S. typhimurium* strains TA1537 and TA1538 either in the presence or the absence of metabolic activation [HID = 74000 µg/plate (500 µmol/plate)].

5.2 Lower Eukaryotic Systems

In *S. cerevisiae*, TCP induced mitotic gene conversion (at least 2-fold) at both the histidine and tryptophan loci in the presence but not the absence of metabolic activation [LED not provided, HID = 5000 mg/mL (34,000 μM)] (Dean and Brooks, 1979).

5.3 Mammalian Systems *In Vitro*

5.3.1 DNA Damage

Williams et al. (1989; cited by IARC Vol. 63, 1995) reported that TCP did not induce UDS in primary rat hepatocytes [HID = 10.0 μg/mL (67.8 μM)].

Von der Hude et al. (1987; cited by IARC, 1995) reported TCP induced a significant increase in SCE in Chinese hamster lung V79 cells in the presence but not the absence of metabolic activation [LED = 44.0 μg/mL (298 μM)].

NTP (1993) reported that TCP induced SCE in CHO cells in the presence [LED = 14.2 μg/mL (96.3 μM)] but not the absence [HID = 141.7 μg/mL (961 μM)] of S9 activation.

5.3.2 Gene Mutations

In an unpublished study (a TSCA 8d submission to the U.S. EPA), Sawin and Hass (1982a,b) reported that exposure to TCP in the presence but not the absence of metabolic activation induced forward mutations at the *tk* locus of mouse lymphoma L5178Y cells. This occurred with activation, LED = 2.4 μg/mL (16 μM), and without activation, HID = 560 μg/mL (3800 μM)]. Using the same mouse lymphoma L5178Y mutational assay, NTP (1993) also reported that treatment with TCP for 4 hours induced forward mutations at the *tk* locus in the presence [LED = 14.0 μg/mL (95.0 μM)] but not the absence [HID = 700 μg/mL (4750 μM)] of metabolic activation.

5.3.3 Chromosomal Damage

The frequency of chromosomal aberrations was not increased in rat liver (RL_4) cells treated with TCP in the absence of metabolic activation [HID = 1000 μg/mL (6800 μM)] (Dean and Brooks, 1979). In contrast, as reviewed by IARC (1995), the U.S. NTP (1993) reported that TCP induced chromosomal aberrations in CHO cells only in the presence of metabolic activation [LED = 60 μg/mL (407 μM)]. Doherty et al. (1996) reported that exposure to TCP at 10 to 5000 μM for one cell cycle induced micronuclei in 3 human lymphoblastoid cell lines expressing cytochromes CYP1A1, CYP1A2, and CYP2E1. Cultures were tested in the presence of cytochalasin B and the absence of metabolic activation. An 8-fold increase at the top dose in primarily kinetochore-negative micronuclei (i.e., resulting from structural chromosomal damage) over controls was observed (LED = 1000 μM).

5.3.4 Cell Transformation

Hatch et al. (1983; cited by IARC, 1995) reported that TCP enhanced morphological transformations in Syrian hamster embryo by simian adenovirus SA7 virus in the absence of metabolic activation (dose levels and exposure time were not provided).

5.4 Mammalian Systems *In Vivo*

5.4.1 DNA Damage

Mirsalis et al. (1983; cited by IARC, 1995) reported that TCP (dose levels and route of exposure not provided) did not induce UDS in male Fischer 344 rat hepatocytes in the absence of metabolic activation. Using alkaline elution, Weber and Sipes (1990; cited by IARC, 1995) found that male Fischer 344 rats administered TCP at 30, 100, and 300 mg/kg i.p. induced hepatic DNA damage [LED = 30 mg/kg (200 μmol/kg)] but not DNA-protein cross-links [HID = 300 mg/kg (2030 μmol/kg)]. Weber and Sipes (1990; cited by IARC, 1995) also found that male Fischer 344 rats administered [^{14}C]TCP at 30 mg/kg i.p. induced hepatic covalent DNA binding. La et al. (1995) reported that male B6C3F$_1$ mice and Fischer 344 rats administered TCP via gavage [3 and 30 mg/kg (20 and 200 mmol/kg) for mice or 6 and 60 mg/kg (41 and 410 mmol/kg) for rats] induced DNA adducts in several tissues 6 hours after administration. The highest levels of adducts were found in the stomach, kidney, pancreas, and liver for mice [LED = 30 mg/kg (200 μmol/kg)] and the liver, kidney, pancreas, tongue, and stomach for rats [LED = 60 mg/kg (410 μmol/kg)].

5.4.2 Gene Mutations

Saito-Suzuki (1982; cited by IARC, 1995) reported that TCP at an oral dose of 80.0 mg/kg (543 μmol/kg) did not induce dominant lethal mutations in male Sprague-Dawley rats.

5.5 Trichloropropane Metabolites

5.5.1 1,3-Dichloro-2-propanol (MW = 128.986)

As reviewed by IARC (1995), Hahn et al. (1991) found that 1,3-dichloro-2-propanol, tested only in the absence of S9 activation, induced SOS repair as measured by the chromo test in *E. coli* strain PQ37 [LED = 369 μg/plate (2.86 μmol/plate)]. Hahn et al (1991) also reported that 1,3-dichloro-2-propanol induced gene mutations in *S. typhimurium* strains TA100 [LED = 1164 μg/plate (9.02 μmol/plate)] and TA1535 [LED = 384 μg/plate (2.98 μmol/plate)] in both the presence and absence of metabolic activation. Von der Hude et al. (1988, cited by IARC, 1995) found that SCE were induced by 1,3-dichloro-2-propanol in Chinese hamster lung V79 cells in both the presence and absence of metabolic activation [LED = 147.4 μg/mL (1143 μM)].

5.5.2 1,3-Dichloroacetone (MW = 126.970)

As reviewed by IARC (1995), Le Curieux et al. (1994) found that 1,3-dichloroacetone induced SOS repair as measured by the chromo test in *E. coli* strain PQ37 [LED = 0.7 μg/plate (0.005 μmol/plate)] both in the presence and absence of metabolic activation. IARC (1995) reported on 3 microbial mutagenicity studies with 1,3-dichloroacetone. It was mutagenic in *S. typhimurium* strains TA100 and TA1535 with or without metabolic activation [LED = 1.6 μg/plate (0.0054 μmol/plate)]. It was not mutagenic in *S. typhimurium* strain TA98 in the presence or absence of metabolic activation [HID = 10 μg/plate (7.9 μmol/plate)] (Meier et al., 1985; cited by IARC, 1996). Von der Hude et al. (1988; cited by IARC, 1995) reported that SCE were induced by 1,3-dichloroacetone in Chinese hamster lung V79 cells in both the presence and absence of metabolic activation [LED = 0.3 μg/mL (2 μM)]. Le Curieux et al. (1994; cited by IARC, 1995) also reported that 1,3-dichloroacetone induced micronuclei in peripheral blood erythrocytes of the newt *Pleurodeles waltl* [LED = 0.03 mg/kg (0.2 μmol/kg) for 12 days].

Table 5-1. Summary of 1,2,3-Trichloropropane Genotoxicity Studies

Test System	Biological Endpoint	S9 Metab. Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
5.1 Noneukaryote Systems							
5.1.1 DNA Damage							
Escherichia coli strain PQ37	SOS repair induction (chromo test)	+/-	n.p.	n.g.	negative/ negative	Experimental details were not given.	von der Hude et al. (1988; cited by IARC, 1995)
5.1.2 Gene Mutations							
E. coli repair deficient strain WP2*uvr*A and repair proficient strain WP2	gene mutations	+/-	n.p.	0.2 - 2000 µg/plate (0.0014 - 14 µmol/plate)	positive/ negative - WP2*uvr*A; negative/ negative - WP2	+S9 LED = 2000 µg (14 µmol)/plate for WP2*uvr*A, HID = 2000 µg (14 µmol)/plate for WP2*uvr*A -S9 and WP2 ÅS9	Dean and Brooks (1979)
Salmonella typhimurium strains TA100, TA98, TA1535, TA1537, and TA1535	*his* gene mutations	+/-	n.p.	0.2 - 2000 µg/plate (0.0014 µmol - 14 µmol)/plate)	positive/ positive - TA1535; positive/ negative for other strains	Weakly positive (2.7- to 4.6-fold) in TA1535 -S9 [LED = 200 µg (1.4 µmol)/plate] and strongly positive (16.6- to 35.5-fold) +S9 [LED = 20 µg (0.14 µmol)/plate]. HID = 2000 µg (14 µmol)/plate for other strains ±S9	Dean and Brooks (1979)
S. typhimurium strains TA100, TA97, TA98, and TA1535	*his* gene mutations	+/-	n.p.	n.g.	positive/ negative	Positive only in the presence of metabolic activation [LED = 5.5 µg/plate (0.04 µmol/plate)]. HID without S9 was not provided.	5 papers cited by IARC (1995)

Table 5-1. Summary of 1,2,3-Trichloropropane Genotoxicity Studies (Continued)

Test System	Biological Endpoint	S9 Metab. Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
S. typhimurium strains TA1537, and TA1538	*his* gene mutations	+/-	n.p.	n.g.	negative/ negative	HID = 74 µg/plate (500 µmol/plate)	Ratplan and Plaumann (1988; cited by IARC, 1995)
5.2 Lower Eukaryote Systems							
Saccharomyces cerevisiae	mitotic gene conversion at histidine and tryptophan loci	+/-	n.p.	10 - 5000 µg/mL (70 to 34,000 µM)	positive/ negative	Treatment was for 1 to 4 h; LED not provided, HID = 500 µg/mL (34,000 µM)	Dean and Brooks (1979)
5.3 Mammalian Systems *In Vitro*							
5.3.1 DNA Damage							
primary rat hepatocytes	Unscheduled DNA synthesis (UDS)	NA	n.p.	n.g.	negative	LED = 10.0 µg/mL (67.8 µM)	Williams et al. (1989; cited by IARC, 1995)
Chinese hamster lung V79 cells	sister chromatid exchanges (SCE)	+/-	n.p.	n.g.	positive/ negative	+S9 LED = 44.0 µg/mL (298 µM)	von der Hude et al. (1987; cited by IARC, 1995)
Chinese hamster ovary (CHO) cells	SCE	+/-	n.p.	+S9 = 1.42 to 59.5 µg/mL (9.6 to 404 µM) for 2 h -S9 = 14.2 to 141.7 µg/mL (96.3 to 961 µM) for 25 h	positive/ negative	+S9 LED = 14.2 µg/mL (96.3 µM); -S9 HID = 141.7 µg/mL (961 µM).	NTP (1993) & IARC (1995)

Table 5-1. Summary of 1,2,3-Trichloropropane Genotoxicity Studies (Continued)

Test System	Biological Endpoint	S9 Metab. Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
5.3.2 Gene Mutations							
mouse lymphoma L5178Y cells	*tk* gene mutations	+/-	n.p.	+S9 = 75 - 560 µg/mL (510 - 3800 µM) -S9 = 2.4 - 18 µg/mL (16 - 120 µM)	positive/ negative	+S9 LED = 2.4 µg/mL (16 µM); -S9 HID = 560 µg/mL (3800 µM).	Sawin and Hass (1982a,b)
mouse lymphoma L5178Y cells	*tk* gene mutations	+/-	n.p.	2.8 to 84.0 µg/mL (19 to 570 µM) +S9 & 10.9 to 700 µg/mL (74 to 4750 µM) - S9 for 4 h.	positive/ negative	+S9 LED = 14.0 µg/mL (95.0 µM); -S9 HID = 700 µg/mL (4750 µM).	NTP (1993) & IARC (1995)
53.3 Chromosomal Damage							
Rat liver RL_4 cells	chromosome aberrations	NA	n.p.	250-1000 µg/mL (1700 to 6800 µM)	negative	HID = 1000 µg/mL (6800 µM)	Dean and Brooks (1979)
Chinese hamster ovary (CHO) cells	chromosome aberrations	+/-	n.p.	+S9 = 60.0 to 90.7 µg/mL (407 to 615 µM) for 2 h -S9 = 870 to 1077 µg/mL (5900 to 7305 µM) for 8 h.	positive/ negative	+S9 LED = 60.0 µg/mL (407 µM); -S9 HID = 1077 µg/mL (7305 µM).	NTP (1993) & IARC (1995)
human lymphoblastoid cell lines AHH- 1, MCL-5, and h2E1 expressing cytochromes CYP1A1, CYP1A2, and CYP2E1	induction of kinetochore positive/negative micronuclei in cytochalasin B-blocked cells	NA	n.p.	10 to 5000 µM for one cell cycle	positive	TCP produced an 8-fold induction in micronuclei at the top dose over controls, the majority of which stained kinetochore negative. LED = 1000 µM	Doherty et al. (1996)

Table 5-1. Summary of 1,2,3-Trichloropropane Genotoxicity Studies (Continued)

Test System	Biological Endpoint	S9 Metab. Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
5.3.4 Cell Transformation							
Syrian hamster embryo (SHE) SA7 cells	morphological transformation	-	n.p.	n.g.	positive	No experimental details given.	Hatch et al. (1983; cited by IARC, 1995)
5.4 Mammalian Systems *In Vivo*							
5.4.1 DNA Damage							
male Fischer 344 rat hepatocytes	UDS	NA	n.p.	n.g.	negative	Route of exposure not provided.	Mirsalis et al. (1983; cited by IARC, 1995)
male Fischer 344 rat hepatocytes	DNA damage (alkaline elution)	NA	n.p.	30, 100, & 300 mg/kg i.p. (203.5 to 2035 µmol/kg)	positive	LED = 30.0 µg/kg (200 µmol/kg)	Weber and Sipes (1990; cited by IARC, 1995)
male Fischer 344 rat hepatocytes	DNA-protein crosslinks (alkaline elution)	NA	n.p.	30, 100, & 300 mg/kg i.p. (200 to 2030 µmol/kg)	negative	HID = 300.0 µg/kg (2035 µmol/kg)	Weber and Sipes (1990; cited by IARC, 1995)
male Fischer 344 rat hepatocytes	covalent DNA binding (method not provided)	NA	n.p.	30 mg/kg [^{14}C]TCP i.p. (200 µmol/kg)	positive	Length of exposure not provided.	Weber and Sipes (1990; cited by IARC, 1995)

Table 5-1. Summary of 1,2,3-Trichloropropane Genotoxicity Studies (Continued)

Test System	Biological Endpoint	S9 Metab. Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
male B6C3F$_1$ mice	DNA adducts (HPLC elution)	NA	n.p.	3 & 30 mg/kg [^{14}C]TCP (20 to 200 μmol/kg) by gavage	positive	Animals were sacrificed 6 hours after administration and 9 target organs/tissues analyzed for DNA adducts. Highest adduct levels were found in stomach, kidney and liver. LED = 30 mg/kg (200 μmol/kg)	La et al. (1995)
male Fischer 344 rat	DNA adducts (HPLC elution)	NA	n.p.	60 & 600 mg/kg [^{14}C]TCP (41 and 410 μmol/kg) by gavage	positive	Animals were sacrificed 6 hours after administration and 7 target organs/tissues analyzed for DNA adducts. Highest adduct levels were found in liver, kidney, pancreas, tongue, and stomach. LED = 60 mg/kg (410 μmol/kg)	La et al. (1995)
5.4.2 Gene Mutations							
male Sprague-Dawley rats	dominant lethal mutations	NA	n.p.	80.0 mg/kg/day p.o. bw for 5 days (543 μmol/kg)	negative		Saito-Suzuki (1982; cited by IARC, 1990)

Table 5-2. Summary of 1,2,3-Trichloropropane Metabolite Genotoxicity Studies

Test System	Biological Endpoint	S9 Metab. Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
5.5 1,2,3-Trichloropropane Metabolites							
5.5.1 1,3-Dichloro-2-propanol							
E. coli strain PQ37	SOS repair induction (chromo test)	-	n.p.	n.g.	positive	LED = 369 µg/plate (2.86 µmol/plate)	Hahn et al. (1991; cited by IARC, 1995)
S. typhimurium strains TA100 and TA1535	*his* gene mutations	+/-	n.p.	n.g.	positive/ positive	LED (TA100) = 1164 µg/plate (9.02 µmol/plate); LED (TA1535) = 384 µg/plate (2.98 µmol/plate).	Hahn et al. (1991; cited by IARC, 1995)
Chinese hamster lung V79 cells	SCE	+/-	n.p.	n.g.	positive/ positive	LED = 147.4 µg/mL (1143 µM)	von der Hude et al. (1987; cited by IARC, 1995)
5.5.2 1,3-Dichloroacetone							
E. coli strain PQ37	SOS repair induction (chromo test)	+/-	n.p.	n.g.	positive/ positive	LED = 0.7 µg/plate (0.005 µmol/plate)	Le Curieux et al. (1994; cited by IARC, 1995)
S. typhimurium strains TA100 and TA1535	*his* gene mutations	+/-	n.p.	n.g.	positive/ positive	LED = 1.6 µg/plate (0.013 µmol/plate)	3 papers cited by IARC (1995)
S. typhimurium strain TA98	*his* gene mutations	+/-	n.p.	n.g.	negative/negative	HID = 10 µg/plate (7.9 µmol/plate)	Meier et al. (1985; cited by IARC 1995)
Chinese hamster lung V79 cells	SCE	+/-	n.p.	n.g.	positive/ positive	LED = 0.3 µg/mL (2 µM)	von der Hude et al. (1988; cited by IARC, 1995)
Pleurodeles waltl (newt)	micronucleus induction in peripheral blood erythrocytes	NA	n.p.	n.g.	positive	LED = 0.03 mg/kg (0.2 µmol/kg) for 12 days	Le Curieux et al. (1994; cited by IARC, 1995)

Abbreviations: HID = highest ineffective dose; LED = lowest effective dose; NA = not applicable; n.g. = not given; n.p. = not provided

Figure 5-1. Genetic Activity Profile of 1,2,3-Trichloropropane (Data limited to IARC, 1995)

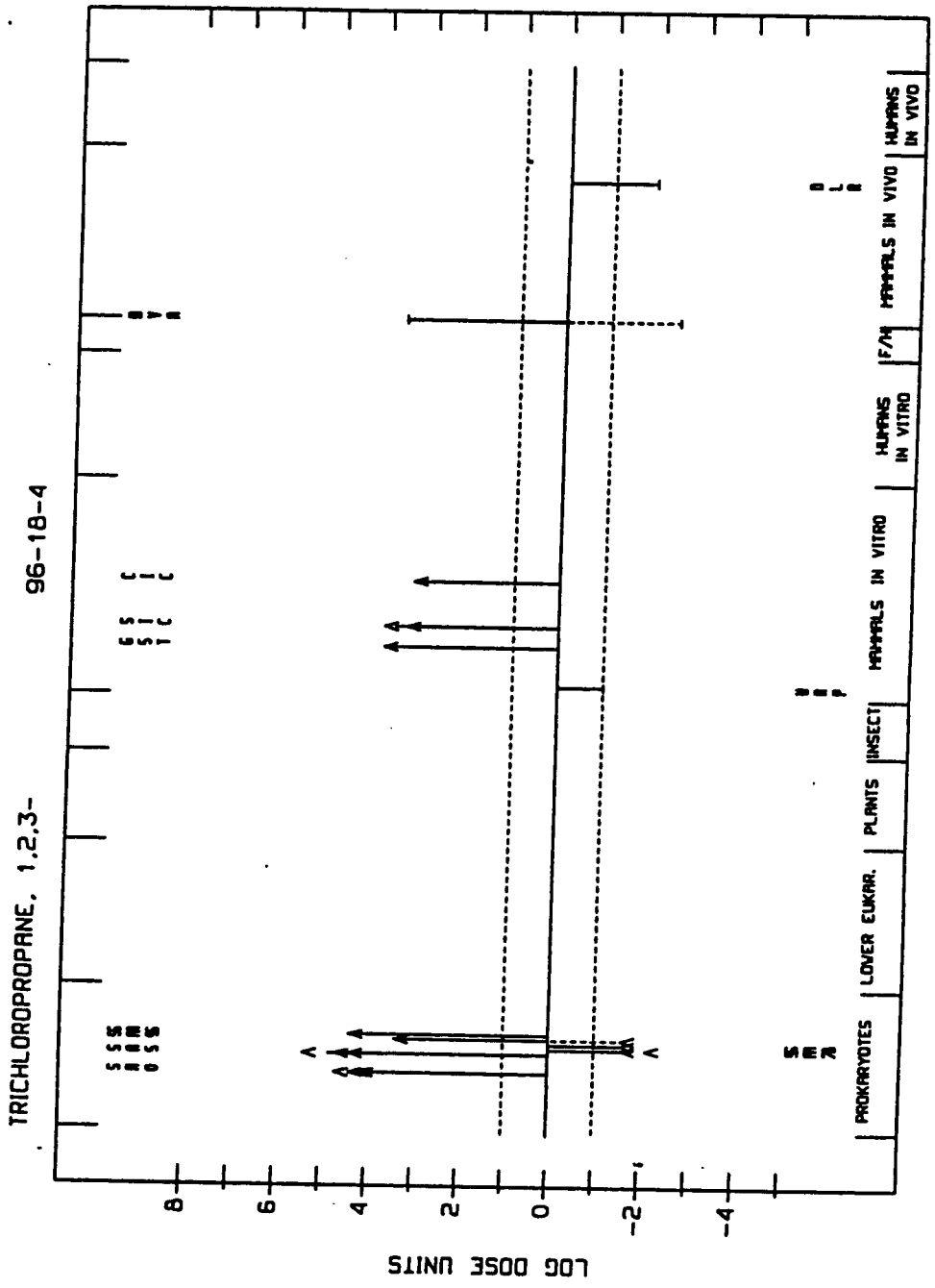
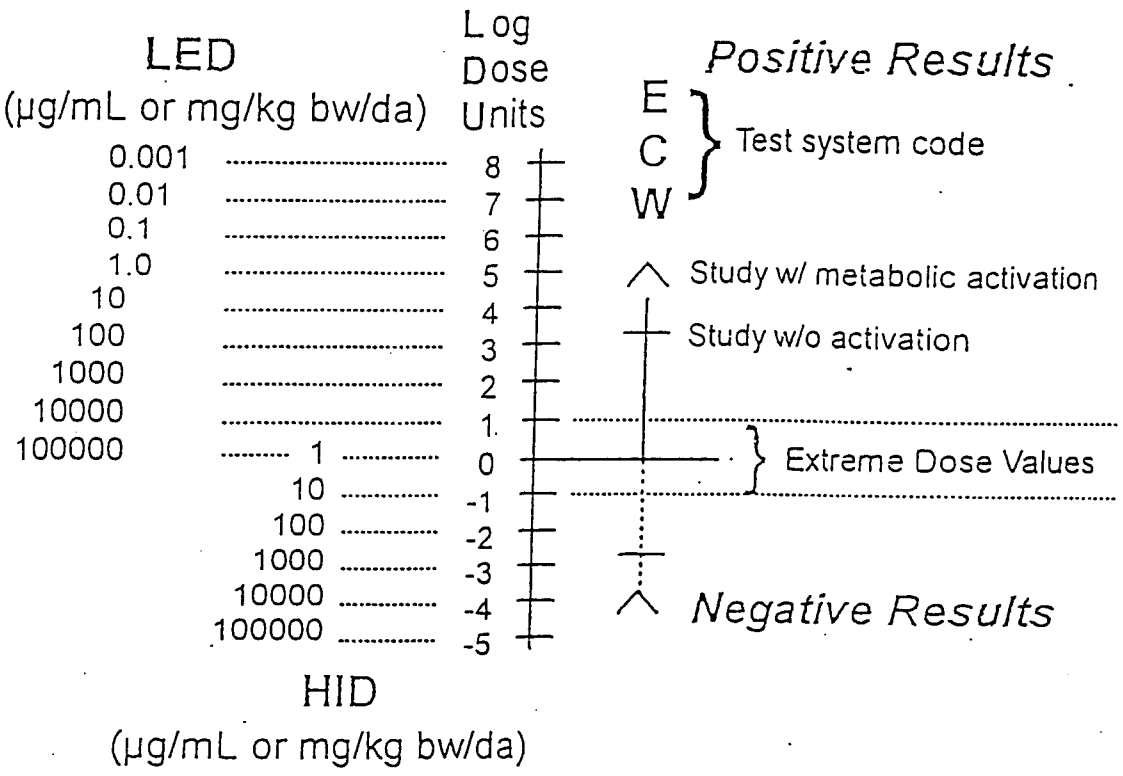


Figure 5-2. Schematic View of a Genetic Activity Profile (GAP)



A schematic view of a Genetic Activity Profile (GAP) representing four studies (two positive and two negative) for an example short-term test, ECW. Either the lowest effective dose (LED) or the highest ineffective dose (HID) is recorded from each study, and a simple mathematical transformation (as illustrated above) is used to convert LED or HID values into the logarithmic dose unit (LDU) values plotted in a GAP. For each test, the average of the LDUs of the majority call is plotted using a solid vertical bar drawn from the origin. A dashed vertical bar indicates studies that conflict with the majority call for the test. Note in cases where there are an equal number of positive and negative studies, as shown here, the overall call is determined positive. The GAP methodology and database have been reported previously (Garrett et al., 1984; Waters et al., 1988, 1991).

Garrett, N.E., H.F. Stack, M.R. Gross, and M.D. Waters. 1984. An analysis of the spectra of genetic activity produced by known or suspected human carcinogens. Mutat. Res. 143:89-111.

Waters, M.D., H.F. Stack, A.L. Brady, P.H.M. Lohman, L. Haroun, and H. Vainio. 1988. Use of computerized data listings and activity profiles of genetic and related effects in the review of 195 compounds. Mutat. Res. 205:295-312.

Waters, M.D., H.F. Stack, N.E. Garrett, and M.A. Jackson. 1991. The genetic activity profile database. Environ. Health Perspect. 96:41-45.

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism, and Excretion

Summary: In rodents, TCP is metabolized via cytochrome P-450 oxidation or conjugated with glutathione to over 10 metabolites. *In vitro* experiments with rat and human liver microsomes indicated that human incubations produced the major mutagenic metabolite 1,3-dichloroacetone found in rat incubations. The rates of tissue distribution, excretion, and the percentage of radiolabel eliminated were the same for mice and rats, although mice metabolized and excreted TCP more rapidly than rats. Other than the data presented below, there are no other human data to compare TCP metabolic pathways between humans and rodents. These data suggest that humans metabolize TCP to a similar reactive species found in rats, although it is produced at a slower rate.

6.1.1 Metabolism

Structures of many of the TCP metabolites are shown in the metabolic pathways depicted in Figure 6-1. Experimental details of the studies discussed in this section are presented in Table 6-1 (1,2,3-Trichloropropane Metabolite and Adduct Identification).

Rat and mouse *in vivo* experiments have shown that the metabolism of TCP involves both conjugation with glutathione and oxidation by cytochrome P-450, producing over 10 metabolites (Mahmood et al., 1991; Weber and Snipes, 1992; Irwin et al., 1995). The major metabolite identified in exhaled breath of mice and rats gavaged with TCP in corn oil was CO_2 (see table for postulated metabolic pathways for CO_2 production). Both mice and rats produced the metabolite *N*-acetyl-(3-chloro-2-hydroxypropyl)-L-cysteine (ACPC); however, ACPC accounted for only 3% of the radioactive metabolites in cumulative 6-hour male mouse urine, while in the 6-hour male rat urine, ACPC accounted for 40% of the radioactive metabolites (Mahmood et al., 1991; see section 6.3.2).

In vitro experiments with human and rat liver microsomal preparations in the presence of TCP showed that 1,3-dichloroacetone (DCA) was formed at a faster rate in rat incubations (0.27 nmol/min/mg protein) than in human microsomal incubations (0.03 nmol/min/mg protein), suggesting that human liver is capable of metabolizing TCP to a mutagenic species in humans (Weber and Snipes, 1992; see section 6.3 for mechanistic relevance).

No other human data were found to compare TCP metabolic pathways between humans and rodents.

6.1.2 Absorption, Distribution, and Excretion

6.1.2.1 Mice

Following gavage doses of 30 mg/kg bw or 60 mg/kg bw in corn oil to male B6C3F$_1$ mice, [2-^{14}C]TCP was extensively absorbed and rapidly metabolized and excreted. The highest concentrations of radiolabel were found in forestomach, kidney, and liver within 60 hours. The concentrations of radiolabel in most tissues were proportional to the dose. Within 24 hours, more than 50% of the administered radiolabel was recovered in urine, feces, and as $^{14}CO_2$ in exhaled breath. Within 60 hours of dose administration, 20% of the dose was exhaled as $^{14}CO_2$ and less than 1% as TCP, 65% was excreted in urine, and 15% excreted in feces. Note that male mice exhaled $^{14}CO_2$ at a significantly faster rate than male (or female) rats within the first 24-36 hours after administration of the dose (see section 6.3 for further elaboration on possible

mechanistic inferences). No significant effect on the excretion of TCP-derived radioactivity in feces, urine, and in expired air of mice was observed when the dose was doubled. *N*-Acetyl-*S*-(3-chloro-2-hydroxypropyl)-*L*-cysteine accounted for ~3% of the total urinary radiolabel, with no other metabolites identified in the urine (Mahmood et al., 1991).

6.1.2.2 Rats

[1,3-^{14}C]TCP was rapidly absorbed, distributed, and eliminated from F344 rats i.v. administered a single dose of 3.6 mg/kg bw [1,3-^{14}C]TCP in a mixture of Emulphor EL-620, ethanol, and water. The initial half-life of the unchanged compound in the blood was 0.29 hour and the terminal half-life was 23 hours. Within 15 minutes, 37% of the dose accumulated in the adipose tissue. Four hours after dose administration, the liver contained the largest fraction of the dose, primarily as metabolites. Within 24 hours, ~90% of the dose was excreted—40% via urine, 30% in expired air (25% exhaled as $^{14}CO_2$, and 5% exhaled as unchanged [1,3-^{14}C]TCP), and 18% excreted in feces. Urine contained no detectable TCP. Although none of the urinary and biliary metabolites were identified, each accounted for less than 10% of the administered dose (Volp et al., 1984).

[2-^{14}C]TCP was rapidly absorbed, metabolized, and excreted following gavage (single dose; 30 mg [200 μg/kg bw in corn oil) to male and female F344 rats. In male rats, the highest concentration (μg eq/g tissue) was found in the tissue of the forestomach , followed by the glandular stomach, intestine, fat, liver, and kidney 6 hours after treatment. Thereafter, the concentrations of TCP-derived radioactivity declined in the forestomach, fat, intestines, glandular stomach, spleen, and lungs of male rats (Mahmood et al., 1991).

Radiolabel derived from [2-^{14}C]TCP was concentrated in the liver, kidney, and forestomach 60 hours after administration of the dose to males and females. In female rat tissues, the concentration of radioactivity was higher than that of males; however, only in spleen and forestomach were the differences significant. No significant differences in concentrations of TCP-derived radioactivity were seen in male and female rats 24 hours after dose administration (Mahmood et al., 1991).

Ninety percent or more of the TCP-derived radioactivity was excreted within 60 hours after administration of the dose in male and female rats. No significant differences in the routes of elimination between male and female rats or male mice and male rats were observed in relation to the percentage of radiolabel ultimately eliminated by urine, feces, and expired breath. Urinary excretion was the major route of elimination; male and female rats excreted approximately 57 and 50%, respectively, via this route. Twenty percent of the dose was eliminated in feces, with similar concentrations found as $^{14}CO_2$ in expired breath. Within 24 hours, more than 50% of the dose was detected in urine, feces, and in exhaled breath as $^{14}CO_2$. Male mice exhaled $^{14}CO_2$ at a significantly faster rate than male rats within the first 24-36 hours after administration of the dose (see subsection 6.3 for mechanistic implications). ACPC accounted for 40% of the radioactive metabolites in the 6-hour rat urine, as opposed to ~3% in mouse urine. Another metabolite, *S*-(3-chloro-2-hydroxypropyl)-*L*-cysteine (CPC), was identified in male rat 6-hour and female rat 24-hour urine. In the rat 6-hour bile, 2-(*S*-glutathionyl)malonic acid (GMA) displayed the largest peak (60%) when all three metabolites were analyzed by HPLC (Mahmood et al., 1991).

6.2 Pharmacokinetics

No human data were available to compare with rodent pharmacokinetics.

6.3 Modes of Action

Summary: Human liver microsomes are capable of metabolizing TCP to a DNA- reactive species similar to those found in rats showing neoplastic responses in the NTP bioassay. TCP must be metabolized to a reactive species before inducing gene mutations, chromosomal aberrations, and micronuclei. The differing response (neoplastic and proliferative effects) in rats and mice in the NTP bioassay did not appear to be the result of major differences in the way the two species metabolize TCP. There are no data suggesting that the carcinogenic mechanism operating in rodents would not also operate in humans.

The genotoxicity activity profile (see section 5.0 and Figure 5-1) indicates that TCP must be metabolized to a reactive species before inducing gene mutations in *Salmonella typhimurium;* SCE in both Chinese hamster ovary and lung V79 cells; micronuclei in human lymphoblastoid cells; chromosomal aberrations in CHO cells; and gene mutations in mouse lymphoma cells. DCA, the major rat *in vitro* mutagenic metabolite of TCP, has also been identified in human microsomal preparations. The rate of DCA formation in rat microsomal incubations was 0.27 nmol/min/mg protein, while human microsomal exposures produced DCA at a rate of 0.03 nmol/min/mg protein, indicating that human liver microsomes are capable of metabolizing TCP to a DNA reactive species similar to that found in rats, which have shown neoplastic responses in the NTP bioassay of TCP (discussed in Section 4.0).

TCP was found to be a more potent carcinogen in rats than in mice. Rats produced neoplastic and proliferative responses at more sites and at lower doses than mice in the NTP bioassay. As suggested by a companion study conducted by Mahmood et al. (1991; see subsection 6.1), the differing response (neoplastic and proliferative effects) in rats and mice did not appear to be the result of major differences in the way the two species metabolize TCP (Irwin et al., 1995). Note that Mahmood et al. (1991) studied the disposition and metabolism of 2-[^{14}C]-1,2,3-TCP in B6C3F$_1$ mice and F344 rats over the dose range used for the NTP 2-year bioassay (3, 10, or 30 mg/kg in rats [20, 68, or 200 μmol/kg] and 6, 20, or 60 mg/kg [41, 140, or 440 μmol] in mice). The tissue distribution, routes of excretion, and the percentage of radiolabel ultimately eliminated were the same for mice and rats, although mice metabolized and excreted TCP more rapidly than rats (Mahmood et al., 1991).

No data are available that would suggest that the mechanisms thought to account for tumor induction by TCP in experimental animals would not also operate in humans.

6.4 Structure-Activity Relationships

Summary: 1,2-Dibromo-3-chloropropane (DBCP) was found to be a potent multi-organ carcinogen in rats and mice when administered by gavage or inhalation. TCP and DBCP share some common metabolic pathways. Like DBCP, the toxic effects of TCP could have resulted from bioactivation to one or more metabolites through oxidation and conjugation, producing the DNA adduct *S*-(1-[hydroxymethyl]-2-(N^7-guanyl)ethyl]glutathione that has been identified in rats exposed to DBCP. The metabolic activation of TCP, 1,2-dibromoethane (EDB), and DBCP has been postulated to occur by a similar mechanism involving glutathione and subsequent

intramolecular rearrangement to form reactive episulfonium ions that are capable of binding to nucleophilic DNA.

6.4.1 Carcinogenicity of Structural Analogues (1,2-Dibromo-3-chloropropane)

The 2-year bioassay (NTP, 1993) was conducted on TCP due to the carcinogenicity of the structurally related compounds 1,2-dibromo-3-chloropropane (DBCP) and ethylene dibromide (EDB) in addition to several other reasons, including its potential for human exposure, and its positive *in vitro* genotoxicity.

DBCP was a potent multi-organ carcinogen in rats and mice when administered by gavage or inhalation (NCI, 1978; NTP, 1982; cited by Irwin et al., 1995). TCP and DBCP share some common metabolic pathways. Like DBCP, the toxic effects of TCP could have resulted from bioactivation to one or more metabolites through oxidation and conjugation, producing the DNA adduct *S*-(1- [hydroxymethyl]-2 (N^7-guanyl)ethyl]glutathione that has been identified in rats exposed to DBCP (Humphreys et al., 1991; cited by Irwin et al., 1995; Mahmood et al., 1991; see Table 6-1). The fact that TCP and DBCP formed *S*-(1- [hydroxymethyl]-2 (N^7-guanyl)ethyl]glutathione *in vivo* suggests that both compounds may be metabolically activated to form a common reactive intermediate (Irwin et al., 1995).

6.4.2 1,2-Dibromoethane (Ethylene Dibromide)

Irwin et al. (1995) found that the metabolic activation of TCP involved glutathione-mediated pathways. A similar mechanism has been described for the metabolic activation of EDB and DBCP that involves conjugation with glutathione and subsequent intramolecular rearrangement to form reactive episulfonium ions that are capable of binding to nucleophilic DNA (Humphreys et al., 1991, Koga et al., 1986, Mahmood et al., 1990; cited by Irwin et al., 1995). One of the major DNA adducts induced by EDB was identified as *S*-(1-[hydroxymethyl]-2-(N^7-guanyl)ethyl]glutathione (Humphreys et al., 1991; cited by Irwin et al., 1995). This adduct was similar to the adduct identified in mice and rats exposed to TCP (Irwin et al., 1995). The results of the studies suggest that the metabolic activation of TCP, EDB, and DBCP occur by a similar mechanism involving glutathione.

6.4.3 Exposure of EDB and DBCP via Gavage

La et al. (1995; cited by Swenberg et al., 1995) found that exposure to bolus doses of TCP via gavage resulted in approximately two times more DNA adducts in kidney, liver, and forestomach than exposure to TCP via drinking water. The authors also found exposure via gavage caused a significant increase in cell proliferation (target organs not given), while exposure via drinking water did not. Studies of EDB and DBCP have reported that the carcinogenic potency of these chemicals is greater when administered by gavage (NTP, 1978; NTP, 1982; NTP, 1983; cited by Irwin et al., 1995).

6.5 Cell Proliferation

Full experimental details for the studies described in this section are presented in Table 6-2.

Summary: In brief, the incidences of pulmonary regeneration and of hyperkeratosis of the forestomach were significantly increased in male and female mice administered TCP by gavage for 125 days. The incidence of squamous hyperplasia of the forestomach was significantly increased in male and female mice administered TCP by gavage for up to 2 years. In male and female rats, the incidences of regenerative renal hyperplasia, chronic inflammation of the nasal turbinates (males only) and bile duct hyperplasia (females only) were significantly increased with administration of TCP by gavage for 125-127 days. In rats administered TCP by gavage for up to 2 years, the incidences of basal cell hyperplasia of the forestomach, squamous hyperplasia of the forestomach, pancreatic hyperplasia, and renal hyperplasia were significantly increased. In rats administered TCP by inhalation, the incidence of focal peribronchial lymphoid hyperplasia was increased in males and females and the incidence of centrilobular to mid-zonal hepatocellular hypertrophy was increased in males only.

6.5.1 Mice

In 50-day-old male and female B6C3F$_1$ mice administered TCP (8, 16, 32, 63, 125, or 250 mg/kg [50–1700 μmol/kg]) by gavage for 125 days, the incidence of pulmonary regeneration was significantly increased in males that received the 2 highest doses and in females that received the 3 highest doses. The incidence of hyperkeratosis of the forestomach was also significantly increased in males that received the 125-mg/kg dose (but not in males that received the 250-mg/kg dose) and in females that received the 3 highest doses (NTP, 1993; Irwin et al., 1995).

In 6-week-old male and female B6C3F$_1$ mice administered TCP (6, 20, or 60 mg/kg [40, 140, or 410 μmol/kg]) by gavage for up to 2 years, the incidence of squamous hyperplasia of the forestomach was significantly increased in all TCP-treated mice (NTP, 1993; Irwin et al., 1995).

6.5.2 Rats

6.5.2.1 Oral Administration

In 57-day-old male and female F344/N rats administered TCP (8, 16, 32, 63, 125, or 250 mg/kg [50-1700 μmol/kg]) by gavage for 125-127 days, the incidence of regenerative renal hyperplasia was significantly increased in rats that received the 125-mg/kg dose (incidence not listed for rats that received the 250-mg/kg [850-μg/kg] dose). The incidence of chronic inflammation of the nasal turbinates was significantly increased in males, but not females, that received the 125-mg/kg dose (incidence not listed for 250-mg/kg group) and the incidence of bile duct hyperplasia was significantly increased in females that received the 125-mg/kg dose (incidence not listed for 250-mg/kg group). The incidence of bile duct hyperplasia was not listed for males (NTP, 1993; Irwin et al., 1995).

In 6-week-old male and female F344/N rats administered TCP (3, 10, or 30 mg/kg [20, 70, or 200 μmol/kg]) by gavage for up to 2 years, the incidence of basal cell hyperplasia of the forestomach was significantly increased in all TCP-treated rats and the incidence of squamous hyperplasia of the forestomach was significantly increased in low-dose and mid-dose males and

in all TCP-treated females. In addition, the incidence of pancreatic hyperplasia was significantly increased in all TCP-treated rats and the incidence of renal hyperplasia was significantly increased in high-dose males and in mid-dose and high-dose females (NTP, 1993; Irwin et al., 1995).

6.5.2.2 Inhalation Exposure

In 7-week-old male and female CD rats administered 5, 15, or 50 ppm TCP 6 hours/day, 5 days/wk, for 13 weeks by inhalation, focal peribronchial lymphoid hyperplasia was detected in the lungs of 6/15 low-dose, 11/15 mid-dose, and 10/15 high-dose males (vs. 0/15 controls; p-value not given) and in 5/15 low-dose, 4/15 mid-dose, and 6/15 high-dose females (vs. 1/15 controls; p-value not given). In low-dose males and females and in mid-dose females, the hyperplasia was considered to be mild. In mid-dose males and in high-dose males and females, the hyperplasia was considered to be more severe. Centrilobular to mid-zonal hepatocellular hypertrophy was also detected in 13/15 low-dose, 15/15 mid-dose, and 15/15 high-dose males (vs. none in controls; p-value not given), but in none of the females. In all rats in which it was detected, the hypertrophy was considered to be mild (Johannsen et al., 1988).

Table 6-1. 1,2,3-Trichloropropane Metabolite and Adduct Identification

Substance	In Vivo Study	In Vitro Study	Reaction/Enzymes	Comments
Parent Compound				
1,2,3-Trichloropropane; TCP (I)			Metabolism of TCP involves both conjugation with glutathione and oxidation. Cytochrome P-450 possibly involved (Mahmood et al., 1991).	CO_2 was the major metabolite found in rats i.v. administered [^{14}C-TCP] (Volp et al., 1984).
Metabolite				
2-Chloroacrolein (II)	Rats and mice (Mahmood et al., 1991; Irwin et al., 1995).		Oxidation by mixed function oxidases (Irwin et al., 1995).	Capable of reacting directly and covalently with cellular components (Irwin et al., 1995).
1,3-Dichloroacetone; DCA (III)		Human and rat liver microsomal incubations in the presence of NADPH (Weber and Sipes, 1992).	Oxygenation at C-2, possibly by a cytochrome P-450-containing monooxygenase, to yield α-chlorohydrin that subsequently loses HCl spontaneously to form 1,3-dichloroacetone (Mahwood et al., 1991). Catalyzed by cytochrome P-450 (Weber and Sipes, 1992).	1,3-Dichloroacetone was formed at a faster rate in rat liver microsomal incubations (0.27 nmol/min/mg protein) when compared to humans (0.03 nmol/min/mg protein) (Weber and Sipes, 1992).
2-(*S*-Glutathionyl)-malonic acid; GMA (IV)	Rat biliary metabolite (Mahmood et al., 1991).		Conjugated and oxidized (Mahmood et al., 1991).	Major biliary metabolite in rats. The isolation of ACPC from urine, and GMA from bile, suggests both conjugation with glutathione and oxidation of TCP (Mahmood et al., 1991).

Table 6-1. 1,2,3-Trichloropropane Metabolite and Adduct Identification (Continued)

Substance	In Vivo Study	In Vitro Study	Reaction/Enzymes	Comments
N-Acetyl-(3-chloro-2-hydroxypropyl)-L-cysteine; ACPC (V)	Rat and mouse urine (Mahmood et al., 1991).		Further metabolism of 1,3-dichloroacetone via chlorine displacement by glutathione, reduction of the keto group, and further enzymatic modification would form ACPC and CPC. Conjugated and oxidized/cytochrome P-450 possibly involved (Mahmood et al., 1991).	Difference in rat and mouse metabolic rate observed. ACPC accounted for ~3% of urinary radioactive metabolites in male mice as opposed to 40% in 6-h male rat urine (Mahmood et al., 1991).
S-(3-Chloro-2-hydroxypropyl)-L-cysteine; CPC (VI)	Rat urine (Mahmood et al., 1991).		See above Reaction/Enzymes for ACPC.	
Carbon dioxide; CO_2	Mouse expired breath (Mahmood et al., 1991). Rat expired breath (Volp et al., 1984).		Two possible mechanisms for the biotransformation of TCP: TCP metabolized to a tricarboxylic acid cycle intermediate or TCP metabolized to a chlorinated α-keto acid (Mahmood et al., 1991).	25% of the radiolabeled dose was expired as CO_2 following i.v. administration to rats (Volp et al., 1984).
2,3-Dichloro-1-propanol; $HOCH_2CH(Cl)CH_2Cl$		Human and rat liver microsomal incubations in the presence of NADPH and alcohol dehydrogenase (Weber and Sipes, 1992).	Formed from the reduction of 2,3-dichloropropanal; catalyzed by alcohol dehydrogenase (Weber and Sipes, 1992).	Formed at a rate ~ 7 times slower than that of 1,3-dichloro-2-propanol (Weber and Snipes, 1992).

Table 6-1. 1,2,3-Trichloropropane Metabolite and Adduct Identification (Continued)

Substance	In Vivo Study	In Vitro Study	Reaction/Enzymes	Comments
1,3-Dichloro-2-propanol; $ClCH_2CHOHCH_2Cl$		Human and rat liver microsomal incubations in the presence of NADPH and alcohol dehydrogenase (Weber and Sipes, 1992).	1,3-Dichloroacetone reduced to form 1,3-dichloro-2-propanol. Alcohol dehydrogenase catalyzed this reaction (Weber and Sipes, 1992).	
1,3-(2-Propanone)bis(*S*-[*N*-acetylcysteine]); PDM[b]		Human and rat liver microsomal incubations in the presence of *N*-acetylcysteine (Weber and Sipes, 1992).	Conjugate (Weber and Sipes, 1992).	1,3-(2-Propanone)bis-*S,N*-acetylcysteine was the only conjugate detected (Weber and Sipes, 1992).

Table 6-2. Cell Proliferation Induced by 1,2,3-Trichloropropane

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Mice - *Oral Administration*							
50-day-old B6C3F$_1$ mice	20M, 20F per dose	30M, 30F (vehicle alone)	TCP, > 99% pure	8, 16, 32, 63, 125, or 250 mg/kg (50–1700 µmol/kg) in 10 mL corn oil/kg, 5 days/wk by gavage	125 days	An interim evaluation was made at 8 weeks. Surviving mice were killed at the end of the 17-week treatment period and all were necropsied. Complete histopathologic examination was performed on all animals found dead, on all moribund animals that were killed, on all controls, on all males in the 125-mg/kg group, and on all males and females in the 250-mg/kg group. Organs examined from other groups (except the 8-mg/kg group) included spleen (except 16-mg/kg males), lung (except 16-mg/kg males and females and 32-mg/kg males), forestomach (except 16- and 32-mg/kg groups), and liver (125-mg/kg females only). **Lungs:** Positive (for proliferative activity, as indicated by presence of regeneration) The incidence of "regeneration" was significantly increased in males that received the 2 highest doses (in order of increasing dose: 9/12 and 14/19 vs. 0/10 controls [$p < 0.01$, Fisher exact test]) and in females that received the 3 highest doses (in order of increasing dose: 7/9, 10/12, and 7/14 vs. 0/10 controls [$p < 0.01$, Fisher exact test]). At the 8-week interim evaluation, the incidence of regeneration was only significantly increased in females that received the highest dose (5/6 vs. 0/10 controls [$p < 0.01$, Fisher exact test]). **Forestomach:** Positive (for proliferative activity, as indicated by presence of hyperkeratosis) The incidence of hyperkeratosis was significantly increased in males that received the 125-mg/kg dose (7/12 vs. 0/10 controls [$p < 0.01$, Fisher exact test]) and in females that received the 3 highest doses (in order of increasing dose: 7/9, 9/12, 8/14 vs. 0/10 controls [$p < 0.01$, Fisher exact test]). At the 8-week interim evaluation, the incidence of hyperkeratosis was significantly increased in males that received the 125-mg/kg dose (6/8 vs. 0/10 [$p < 0.01$, Fisher exact test]) and in females that received the highest dose (6/6 vs. 4/10 controls [$p < 0.05$, Fisher exact test]).	NTP (1993) Irwin et al. (1995)

Table 6-2. Cell Proliferation Induced by 1,2,3-Trichloropropane (Continued)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
6-wk-old B6C3F$_1$ mice	60M, 60F per dose	60M, 60F (vehicle alone)	TCP, > 99% pure	6, 20, or 60 mg/kg (40, 140, or 410 µmol/kg), 5 days/wk by gavage	103 wk (LD males and male controls) 104 wk (LD females and female controls) 89 wk (MD males and females) 79 wk (HD males) 73 wk (HD females)	Mice were killed at the end of the treatment period. Complete histopathologic examinations were performed on all mice. **Forestomach:** Positive (for proliferative activity, as indicated by presence of hyperplasia) The incidence of squamous hyperplasia was significantly increased in all TCP-treated mice (males: 37/59 LD, 32/60 MD, 38/60 HD vs. 8/60 controls [$p < 0.01$, logistic regression test]; females: 25/60 LD, 23/60 MD, 36/60 HD vs. 11/60 controls [$p < 0.01$, logistic regression test]).	NTP (1993) Irwin et al. (1995)

Table 6-2. Cell Proliferation Induced by 1,2,3-Trichloropropane (Continued)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Rats - *Oral Administration*							
57-day-old F344/N rats	30M, 30F per dose	20M, 20F (vehicle alone)	TCP, > 99% pure	8, 16, 32, 63, 125, or 250 mg/kg (50–1700 µmol/kg) in 5 mL corn oil/kg, 5 days/wk by gavage	125–127 days	An interim evaluation was made at 8 weeks. Surviving rats were killed at the end of the 17-week treatment period and all were necropsied. Complete histopathologic examination was performed on all animals found dead, on all moribund animals that were killed, on all controls, and on all rats in the 125-mg/kg group. At the 8-month interim evaluation, organs examined from 63-mg/kg rats included bone and marrow, heart, kidney, liver, nose, spleen, stomach, and uterus. At the end of the studies, organs examined from 32- and 63-mg/kg rats included adrenal gland (females only), bone and marrow (except 32-mg/kg males), kidneys, liver (except 32-mg/kg females), nose (63-mg/kg rats only), spleen, and thymus (except 32-mg/kg females). All female rats that received 250 mg/kg died by week 2 and all male rats that received this dose died by week 5. **Kidneys:** Positive (for proliferative activity, as indicated by presence of regenerative hyperplasia) The incidence of regenerative hyperplasia was significantly increased in rats that received 125 mg/kg (incidence not listed for rats that received 250 mg/kg) (males: 10/10 vs. 0/20 controls [$p < 0.01$, Fisher exact test; females: 10/11 vs. 0/20 controls [$p < 0.01$, Fisher exact test]). At the 8-week interim evaluation, the incidence of regenerative hyperplasia was significantly increased in rats that received the 3 highest doses (males: 10/10 in 63-mg/kg group, 9/9 in 125-mg/kg group, 9/20 in 250-mg/kg group vs. 0/10 controls [$p < 0.01$, Fisher exact test]; females: 10/10 in 63-mg/kg group, 9/9 in 125-mg/kg group, 4/20 in 250-mg/kg group [$p < 0.01$, Fisher exact test]). **Nasal Turbinates:** Positive (for proliferative activity, as indicated by presence of chronic inflammation; males only) The incidence of chronic inflammation was significantly increased in males, but not females, that received 125 mg/kg (incidence not listed for 250-mg/kg group) (5/9 vs. 0/20 controls [$p < 0.01$, Fisher exact test]). At the 8-week interim evaluation, the incidence of chronic inflammation was not significant. **Bile Ducts:** Positive (for proliferative activity, as indicated by presence of hyperplasia; females only) The incidence of hyperplasia was significantly increased in females that received 125 mg/kg (incidence not listed for 250-mg/kg group) (9/11 vs. 0/20 controls [$p < 0.01$, Fisher exact test]). Incidences were not listed for males. At the 8-week interim evaluation, hyperplasia was detected in 6/9 females that received 125 mg/kg (vs. 0/10 controls [$p < 0.01$, Fisher exact test]), but in none of the femlaes that received 250 mg/kg.	NTP (1993) Irwin et al. (1995)

Table 6-2. Cell Proliferation Induced by 1,2,3-Trichloropropane (Continued)

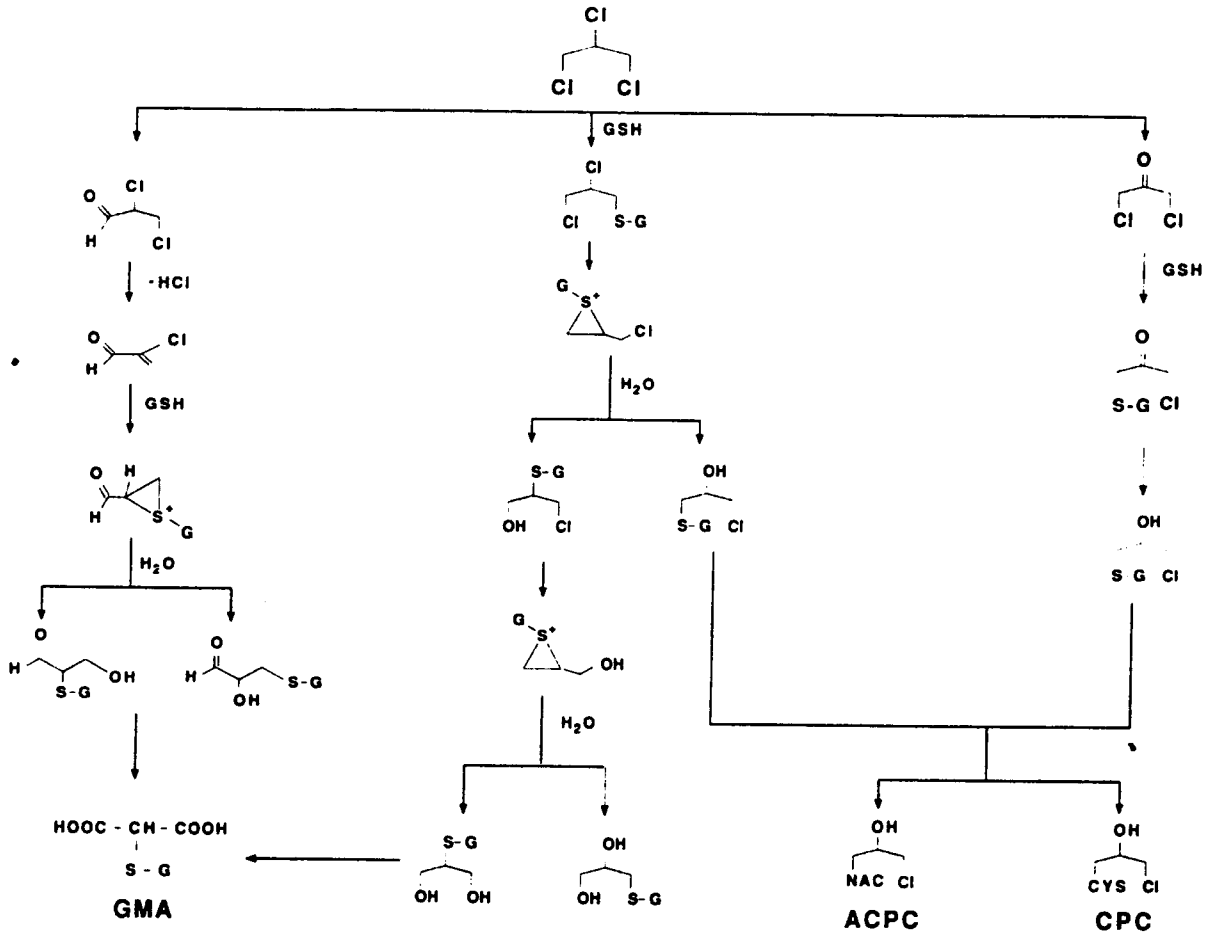
Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
6-wk-old F344/N rats	60M, 60F per dose	60M, 60F (vehicle alone)	TCP, > 99% pure	3, 10, or 30 mg/kg (20, 70, or 200 μmol/kg) 5 days/wk by gavage	103 wk (LD and MD males and male controls) 104 wk (LD and MD females and female controls) 77 wk (HD males) 67 wk (HD females)	Rats were killed at the end of the treatment period. Complete histopathologic examinations were performed on all rats. The life table test and/or logistic regression tests were used to analyze tumor incidence. The life table test "regards neoplasms in animals dying prior to terminal kill as being the cause of death." The logistic regression test "regards these neoplasms as nonfatal." **Forestomach:** Positive (for proliferative activity, as indicated by presence of hyperplasia) The incidence of basal cell hyperplasia was significantly increased (logistic regression test) in all trichloropropane-treated rats (males: 7/60 LD [$p < 0.05$], 12/59 MD [$p < 0.01$], 9/60 HD [$p < 0.01$] vs. 0/60 controls; females: 10/59 LD [$p < 0.01$], 5/59 MD [$p < 0.05$], 9/60 HD [$p < 0.01$] vs. 0/60 controls). The incidence of squamous hyperplasia was significantly increased (logistic regression test) in LD and MD males and in all females (males: 28/60 LD [$p < 0.01$], 13/59 MD [$p < 0.05$] vs. 3/60 controls; females: 26/59 LD, 15/59 MD, 16/60 HD vs. 1/60 controls [$p < 0.01$]). **Pancreas:** Positive (for proliferative activity, as indicated by presence of hyperplasia) The incidence of hyperplasia was significantly increased (logistic regression test) in all trichloropropane-treated rats (males: 48/60 LD, 53/59 MD, 56/60 HD vs. 28/60 controls [$p < 0.01$]; females: 15/59 LD [$p < 0.05$], 24/60 MD [$p < 0.01$], 11/60 HD [$p < 0.01$]). **Kidneys:** Positive (for proliferative activity, as indicated by presence of hyperplasia; MD and HD females, HD males only) The incidence of hyperplasia was significantly increased (logistic regression test) in MD and HD females and in HD males (males: 23/59 MD, 35/60 HD vs. 0/60 controls [$p < 0.01$]; females: 12/59 HD vs. 0/60 controls [$p < 0.01$]).	NTP (1993) Irwin et al. (1995)

Table 6-2. Cell Proliferation Induced by 1,2,3-Trichloropropane (Continued)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Rats - *Inhalation Exposure*							
7-wk-old CD rats	15M, 15F per dose	15M, 15F (exposed to room air in the chambers)	TCP, > 98.9% pure	5, 15, or 50 ppm, 6 h/day, 5 days/wk Exposures were performed in 1-m^3 chambers. Test atmospheres were generated by bubbling dry air through liquid trichloropropane in gas-washing bottles. The resulting vapor was fed into a port on the chamber air intake line and diluted to the exposure concentration with room air.	13 wk	Complete necropsies were performed on all rats that died during the study or were killed at the end of the treatment period. Histopathology examinations were performed on liver, lungs, and spleen tissue. In control and high-dose rats, adrenals, bone and marrow, brain, eyes, gonads, heart, intestines, kidneys, lymph nodes, mammary glands, skeletal muscle, skin, spinal cord, stomach, thyroid, urinary bladder, uterus, and all grossly observable lesions and masses were also examined histopathologically. Incidence data were analyzed by chi-square analysis. If differences were detected, groups were compared using the Fisher exact test. There were no treatment-related deaths. No treatment-related lesions were detected during gross necropsy examination. **Lungs:** Positive (for proliferative activity, as indicated by presence of hyperplasia) Focal peribronchial lymphoid hyperplasia was detected in the lungs of 6/15 LD, 11/15 MD, and10/15 HD males (vs. 0/15 controls; p-value not given) and in 5/15 LD, 4/15 MD, and 6/15 HD females (vs. 1/15 controls; p-value not given). In LD males and females and in MD females, the hyperplasia was considered to be mild. In MD males and in HD males and females, the hyperplasia was considered to be more severe. **Liver:** Positive (for proliferative activity, as indicated by presence of hypertrophy; **males only**) Centrilobular to mid-zonal hepatocellular hypertrophy was detected in 13/15 LD, 15/15 MD, and 15/15 HD males (vs. none in controls; p-value not given), but in none of the females. In all rats in which it was detected, the hypertrophy was considered to be mild.	Johannsen et al. (1988)

Abbreviations: bw = body weight; HD = high dose; LD = low dose; MD = mid dose

Figure 6-1. Possible Metabolic Pathways for the Formation of ACPC, CPC, and GMA from TCP



Source: Mahmood et al. (1991)

7.0 REFERENCES

Dean, B.J., and T.M. Brooks. 1979. *In vitro* Mutation Studies with 1,2,3-Trichloropropane. [TSCA Section 8(e) submission]. U.S. EPA/OTS Public Files. Record Number: 309026. Microfiche Number: 0515727

Doherty, A.T., S. Ellard, E.M. Parry, and J.M. Parry. 1996. An Investigation into the Activation and Deactivation of Chlorinated Hydrocarbons to Genotoxins in Metabolically Competent Human Cells. Mutagenesis 11(3):247-274.

IARC (International Agency for Research on Cancer). 1995. 1,2,3-Trichloropropane. IARC Monogr. Eval. Carcinog. Risks Hum. 63(Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals):223-244.

Irwin, R.D., J.K. Haseman, and S.L. Eustis. 1995. 1,2,3-Trichloropropane: A Multisite Carcinogen in Rats and Mice. Fundam. Appl. Toxicol. 25:241-252.

Johannsen, F.R., and G.J. Levinskas. 1988. Evaluation of the Subchronic and Reproductive Effects of a Series of Chlorinated Propanes in the Rat. I. Toxicity of 1,2,3-Trichloropropane. J. Toxicol. Environ. Health. 25:299-315.

La, D.K., P.D. Lilly, R.J. Anderegg, and J.A. Swenberg. 1995. DNA Adduct Formation in B6C3F$_1$ Mice and Fischer-344 Rats Exposed to 1,2,3-Trichloropropane. Carcinogenesis. 16(6):1419-1424.

Mahmood, N.A., D. Overstreet, and L.T. Burka. 1991. Comparative Disposition and Metabolism of 1,2,3-Trichloropropane in Rats and Mice. Drug Metab. Dispos. 19(2):411-418.

NTP (National Toxicology Program). 1993. Technical Report on the Toxicology and Carcinogenesis Studies of 1,2,3-Trichloropropane (CAS No. 96-18-4) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). NTP TR 384. 348pp.

Sawin, V.L., and B.S. Hass. 1982a. Assay of 1,2,3-Trichloropropane for Gene Mutation in Mouse Lymphoma Cells. [TSCA Sections 8(d) and 8(ecp) submission]. U.S. EPA/OTS Public Files. Record Number: 309014. Microfiche Number: 0515721a

Sawin, V.L., and B.S. Hass. 1982b. Initials Submission: Assay of 1,2,3-Trichloropropane for Gene Mutation in Mouse Lymphoma Cells (Final Report) with Cover Letter Dated 120391. [TSCA Sections 8(d) and 8(ecp) submission]. U.S. EPA/OTS Public Files. Record Number: 420874. Microfiche Number: 0534986b

Volp, R.F., I.G. Sipes, C. Falcoz, D.E. Carter, and J.F. Gross. 1984. Disposition of 1,2,3-Trichloropropane in the Fischer 344 Rat: Conventional and Physiological Pharmacokinetics. Toxicol. Appl. Pharmacol. 75:8-17.

Weber, G.L., and I.G. Sipes. 1992. *In Vitro* Metabolism and Bioactivation of 1,2,3-Trichloropropane. Toxicol. Appl. Pharmacol. 113:152-158.

APPENDIX A

DESCRIPTION OF ONLINE SEARCHES FOR 1,2,3-TRICHLOROPROPANE

DESCRIPTION OF ONLINE SEARCHES FOR 1,2,3-TRICHLOROPROPANE (IARC Monograph in Vol. 63, 1995)

The searches described below were conducted between March and October 1996. An exhaustive search of all pertinent databases was not attempted, but the ones chosen were expected to provide citations for most of the relevant recently published literature. No attempt was made in the search strategy to find toxicity information for metabolites and other structural analogues.

Generally, if an IARC monograph or another authoritative review had been published, literature searches were generally restricted from the year before publication to the current year.

Older literature that needed to be examined was identified from the reviews and original articles as they were acquired. Current awareness was maintained by conducting weekly searches of Current Contents on Diskette® Life Sciences 1200 [journals] edition.

TOXLINE (on STN International): A total of 318 records were in the entire database (1940s to date) indexed by the Chemical Abstracts Service Registry Number (CASRN) 96-18-4 (180 records) or by trichloropropane (unqualified) (217 records). Forty-two records were selected for acquisition of the publications.

CANCERLIT: Twenty-two records in the entire database (1963 to June 1996) were indexed by 1,2,3-trichloropropane or its CASRN. Only 8 had been published since 1990, none of which had not already been identified in other databases.

EMBASE: The same search strategy as described for MEDLINE retrieved 15 records published after 1990. Two new references of interest were selected for acquisition.

EMIC/EMICBACK: Seven records were indexed by the CASRN in EMIC, only one of which had not already been acquired. Nineteen records were indexed by CASRN in EMICBACK.

IRIS: The profile did not include any discussion of carcinogenic effects.

MEDLINE: In the entire database (1966 to 1996), of the 68 records indexed by the unqualified term) "trichloropropane" 22 were prefixed by "1,2,3-" and/or indexed by the CASRN. Only 7 had been published after 1990. No new citations were identified.

NTIS: Government reports on interest identified were already in the contractor's files except for a 1975 OSHA report.

TOXLIT: The same initial search strategy as described for MEDLINE retrieved 86 records published since 1990. These records were further reduced by combining with the truncated (use of ? with the word stem) free text terms in the statement "carcinogen? or mechanis? or

toxicokinetic? or pharmacokinetic? or metaboli? or neoplas? or hyperplas? or metaplas? or foci? or tumor? or tumour?" No new records of interest were identified.

TSCATS (Toxic Substances Control Act Test Submissions): Forty-two records were examined and seven were selected for acquisition.

In September 1996, the contractor performed searches for updating sections 1 and 2, which had been last updated in 1994 with regulatory information from print sources and REGMAT (May 1993 version). REGMAT had broad coverage of EPA regulations, but it is no longer available. Databases searched in 1996 included CSCHEM and CSCORP for U.S. suppliers (databases produced by Chem Sources): HSDB; the Chemical Information System's databases SANSS (the Structure and Nomenclature Search System) and ISHOW (for physical-chemical properties): Chemical Abstracts Service's (CAS) File CHEMLIST for TSCA and SARA updates in 1996; and CAS's CA File sections 59 (Air Pollution and Industrial Hygiene); 60 (Waste Disposal and Treatment), and 61 (Water) for environmental exposure information.

APPENDIX B

LISTING OF GAP TEST CODES IN ALPHABETICAL ORDER

LISTING OF GAP TEST CODES IN ALPHABETICAL ORDER

Test Code	Definition
ACC	Allium cepa, chromosomal aberrations
AIA	Aneuploidy, animal cells in vitro
AIH	Aneuploidy, human cells in vitro
ANF	Aspergillus nidulans, forward mutation
ANG	Aspergillus nidulans, genetic crossing-over
ANN	Aspergillus nidulans, aneuploidy
ANR	Aspergillus nidulans, reverse mutation
ASM	Arabidopsis species, mutation
AVA	Aneuploidy, animal cells in vivo
AVH	Aneuploidy, human cells in vivo
BFA	Body fluids from animals, microbial mutagenicity
BFH	Body fluids from humans, microbial mutagenicity
BHD	Binding (covalent) to DNA, human cells in vivo
BHP	Binding (covalent) to RNA or protein, human cells in vivo
BID	Binding (covalent) to DNA in vitro
BIP	Binding (covalent) to RNA or protein in vitro
BPF	Bacteriophage, forward mutation
BPR	Bacteriophage, reverse mutation
BRD	Other DNA repair-deficient bacteria, differential toxicity
BSD	Bacillus subtilis rec strains, differential toxicity
BSM	Bacillus subtilis multi-gene test
BVD	Binding (covalent) to DNA, animal cells in vivo
BVP	Binding (covalent) to RNA or protein, animal cells in vivo
CBA	Chromosomal aberrations, animal bone-marrow cells in vivo
CBH	Chromosomal aberrations, human bone-marrow cells in vivo
CCC	Chromosomal aberrations, spermatocytes treated in vivo and cytes obs.
CGC	Chromosomal aberrations, spermatogonia treated in vivo and cytes obs.
CGG	Chromosomal aberrations, spermatogonia treated in vivo and gonia obs.
CHF	Chromosomal aberrations, human fibroblasts in vitro
CHL	Chromosomal aberrations, human lymphocyte in vitro
CHT	Chromosomal aberrations, transformed human cells in vitro
CIA	Chromosomal aberrations, other animal cells in vitro
CIC	Chromosomal aberrations, Chinese hamster cells in vitro
CIH	Chromosomal aberrations, other human cells in vitro
CIM	Chromosomal aberrations, mouse cells in vitro
CIR	Chromosomal aberrations, rat cells in vitro
CIS	Chromosomal aberrations, Syrian hamster cells in vitro
CIT	Chromosomal aberrations, transformed animal cells in vitro
CLA	Chromosomal aberrations, animal leukocytes in vivo
CLH	Chromosomal aberrations, human lymphocytes in vivo

Test Code	Definition
COE	Chromosomal aberrations, oocytes or embryos treated in vivo
CVA	Chromosomal aberrations, other animal cells in vivo
CVH	Chromosomal aberrations, other human cells in vivo
DIA	DNA strand breaks, cross-links or rel. damage, animal cells in vitro
DIH	DNA strand breaks, cross-links or rel. damage, human cells in vitro
DLM	Dominant lethal test, mice
DLR	Dominant lethal test, rats
DMC	Drosophila melanogaster, chromosomal aberrations
DMG	Drosophila melanogaster, genetic crossing-over or recombination
DMH	Drosophila melanogaster, heritable translocation test
DML	Drosophila melanogaster, dominant lethal test
DMM	Drosophila melanogaster, somatic mutation (and recombination)
DMN	Drosophila melanogaster, aneuploidy
DMX	Drosophila melanogaster, sex-linked recessive lethal mutation
DVA	DNA strand breaks, cross-links or rel. damage, animal cells in vivo
DVH	DNA strand breaks, cross-links or rel. damage, human cells in vivo
ECB	Escherichia coli (or E. coli DNA), strand breaks, cross-links or repair
ECD	Escherichia coli pol A/W3110-P3478, diff. toxicity (spot test)
ECF	Escherichia coli (excluding strain K12), forward mutation
ECK	Escherichia coli K12, forward or reverse mutation
ECL	Escherichia coli pol A/W3110-P3478, diff. toxicity (liquid susp. test)
ECR	Escherichia coli, miscellaneous strains, reverse mutation
ECW	Escherichia coli WP2 uvrA, reverse mutation
EC2	Escherichia coli WP2, reverse mutation
ERD	Escherichia coli rec strains, differential toxicity
FSC	Fish, chromosomal aberrations
FSI	Fish, micronuclei
FSM	Fish, mutation
FSS	Fish, sister chromatid exchange
FSU	Fish, unscheduled DNA synthesis
GCL	Gene mutation, Chinese hamster lung cells exclusive of V79 in vitro
GCO	Gene mutation, Chinese hamster ovary cells in vitro
GHT	Gene mutation, transformed human cells in vivo
GIA	Gene mutation, other animal cells in vitro
GIH	Gene mutation, human cells in vitro
GML	Gene mutation, mouse lymphoma cells exclusive of L5178Y in vitro
GVA	Gene mutation, animal cells in vivo
G5T	Gene mutation, mouse lymphoma L5178Y cells in vitro, TK locus
G51	Gene mutation, mouse lymphoma L5178Y cells in vitro, all other loci
G9H	Gene mutation, Chinese hamster lung V-79 cells in vitro, HPRT locus
G9O	Gene mutation, Chinese hamster lung V-79 cells in vitro, ouabain resistance
HIM	Haemophilus influenzae, mutation
HMA	Host mediated assay, animal cells in animal hosts

Test Code	Definition
HMH	Host mediated assay, human cells in animal hosts
HMM	Host mediated assay, microbial cells in animal hosts
HSC	Hordeum species, chromosomal aberrations
HSM	Hordeum species, mutation
ICH	Inhibition of intercellular communication, human cells in vitro
ICR	Inhibition of intercellular communication, rodent cells in vitro
KPF	Klebsiella pneumonia, forward mutation
MAF	Micrococcus aureus, forward mutation
MHT	Mouse heritable translocation test
MIA	Micronucleus test, animal cells in vitro
MIH	Micronucleus test, human cells in vitro
MST	Mouse spot test
MVA	Micronucleus test, other animals in vivo
MVC	Micronucleus test, hamsters in vivo
MVH	Micronucleus test, human cells in vivo
MVM	Micronucleus test, mice in vivo
MVR	Micronucleus test, rats in vivo
NCF	Neurospora crassa, forward mutation
NCN	Neurospora crassa, aneuploidy
NCR	Neurospora crassa, reverse mutation
PLC	Plants (other), chromosomal aberrations
PLI	Plants (other), micronuclei
PLM	Plants (other), mutation
PLS	Plants (other), sister chromatid exchanges
PLU	Plants, unscheduled DNA synthesis
PRB	Prophage, induction, SOS repair, DNA strand breaks, or cross-links
PSC	Paramecium species, chromosomal aberrations
PSM	Paramecium species, mutation
RIA	DNA repair exclusive of UDS, animal cells in vitro
RIH	DNA repair exclusive of UDS, human cells in vitro
RVA	DNA repair exclusive of UDS, animal cells in vivo
SAD	Salmonella typhimurium, DNA repair-deficient strains, differential toxicity
SAF	Salmonella typhimurium, forward mutation
SAL	Salmonella typhimurium, all strains, reverse mutation
SAS	Salmonella typhimurium (other misc. strains), reverse mutation
SA0	Salmonella typhimurium TA100, reverse mutation
SA1	Salmonella typhimurium TA97, reverse mutation
SA2	Salmonella typhimurium TA102, reverse mutation
SA3	Salmonella typhimurium TA1530, reverse mutation
SA4	Salmonella typhimurium TA104, reverse mutation
SA5	Salmonella typhimurium TA1535, reverse mutation
SA7	Salmonella typhimurium TA1537, reverse mutation
SA8	Salmonella typhimurium TA1538, reverse mutation

Test Code	Definition
SA9	Salmonella typhimurium TA98, reverse mutation
SCF	Saccharomyces cerevisiae, forward mutation
SCG	Saccharomyces cerevisiae, gene conversion
SCH	Saccharomyces cerevisiae, homozygosis by recombination or gene conversion
SCN	Saccharomyces cerevisiae, aneuploidy
SCR	Saccharomyces cerevisiae, reverse mutation
SGR	Streptomyces griseoflavus, reverse mutation
SHF	Sister chromatid exchange, human fibroblasts in vitro
SHL	Sister chromatid exchange, human lymphocytes in vitro
SHT	Sister chromatid exchange, transformed human cells in vitro
SIA	Sister chromatid exchange, other animal cells in vitro
SIC	Sister chromatid exchange, Chinese hamster cells in vitro
SIH	Sister chromatid exchange, other human cells in vitro
SIM	Sister chromatid exchange, mouse cells in vitro
SIR	Sister chromatid exchange, rat cells in vitro
SIS	Sister chromatid exchange, Syrian hamster cells in vitro
SIT	Sister chromatid exchange, transformed cells in vitro
SLH	Sister chromatid exchange, human lymphocytes in vivo
SLO	Mouse specific locus test, other stages
SLP	Mouse specific locus test, postspermatogonia
SPF	Sperm morphology, F1 mouse
SPH	Sperm morphology, human
SPM	Sperm morphology, mouse
SPR	Sperm morphology, rat
SPS	Sperm morphology, sheep
SSB	Saccharomyces species, DNA breaks, cross-links or related damage
SSD	Saccharomyces cerevisiae, DNA repair-deficient strains, diff. toxicity
STF	Streptomyces coelicolor, forward mutation
STR	Streptomyces coelicolor, reverse mutation
SVA	Sister chromatid exchange, animal cells in vivo
SVH	Sister chromatid exchange, other human cells in vivo
SZD	Schizosaccharomyces pombe, DNA repair-deficient strains, diff. toxicity
SZF	Schizosaccharomyces pombe, forward mutation
SZG	Schizosaccharomyces pombe, gene conversion
SZR	Schizosaccharomyces pombe, reverse mutation
T7R	Cell transformation, SA7/rat cells
T7S	Cell transformation, SA7/Syrian hamster embryo cells
TBM	Cell transformation, BALB/C3T3 mouse cells
TCL	Cell transformation, other established cell lines
TCM	Cell transformation, C3H10T1/2 mouse cells
TCS	Cell transformation, Syrian hamster embryo cells, clonal assay
TEV	Cell transformation, other viral enhancement systems
TFS	Cell transformation, Syrian hamster embryo cells, focus assay

Test Code	Definition
TIH	Cell transformation, human cells in vitro
TPM	Cell transformation, mouse prostate cells
TRR	Cell transformation, RLV/Fischer rat embryo cells
TSC	Tradescantia species, chromosomal aberrations
TSI	Tradescantia species, micronuclei
TSM	Tradescantia species, mutation
TVI	Cell transformation, treated in vivo, scored in vitro
UBH	Unscheduled DNA synthesis, human bone-marrow cells in vivo
UHF	Unscheduled DNA synthesis, human fibroblasts in vitro
UHL	Unscheduled DNA synthesis, human lymphocytes in vitro
UHT	Unscheduled DNA synthesis, transformed human cells in vitro
UIA	Unscheduled DNA synthesis, other animal cells in vitro
UIH	Unscheduled DNA synthesis, other human cells in vitro
UPR	Unscheduled DNA synthesis, rat hepatocytes in vivo
URP	Unscheduled DNA synthesis, rat primary hepatocytes
UVA	Unscheduled DNA synthesis, other animal cells in vivo
UVC	Unscheduled DNA synthesis, hamster cells in vivo
UVH	Unscheduled DNA synthesis, other human cells in vivo
UVM	Unscheduled DNA synthesis, mouse cells in vivo
UVR	Unscheduled DNA synthesis, rat cells (other than hepatocytes) in vivo
VFC	Vicia faba, chromosomal aberrations
VFS	Vicia faba, sister chromatid exchange