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November 1982

Toxic Substances

METABOLISM SUMMARIES OF SELECTED HALOGENATED ORGANIC COMPOUNDS IN HUMAN AND ENVIRONMENTAL MEDIA, A LITERATURE SURVEY

SECOND UPDATE

560/7-82-003
November, 1982

METABOLISM SUMMARIES OF SELECTED HALOGENATED ORGANIC COMPOUNDS IN HUMAN AND ENVIRONMENTAL MEDIA, A LITERATURE SURVEY SECOND UPDATE

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Washington, DC 20460

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TABLE OF CONTENTS

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Introduction

The Office of Pesticides and Toxic Substances' Exposure Evaluation Division (EED) is continuing a preliminary assessment of halogenated organic compounds in human and environmental media. This effort was initiated in 1978 in response to the detection and identification of numerous halogenated hydrocarbons in the environment, notably in drinking water supplies. Although detected levels have generally been low, several halocarbons have entered the environment at relatively high concentrations as a result of accidental spills or contamination of animal feed. The reporting of halogenated pesticides in human blood, serum, and adipose tissue further heightens concern over the potential health effects which may be associated with a halocarbon insult.

This document represents the third in a series of literature surveys[1,2] of the metabolism of halogenated hydrocarbons. These surveys complement EED efforts to evaluate human body burden associated with environmental exposure.

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1 Metabolism Summaries of Selected Halogenated Organic Compounds in Human and Environmental Media, A Literature Survey EPA 560/6-79-008, April 1979.

2 Metabolism Summaries of Selected Halogenated Organic Compounds in Human and Environmental Media, A Literature Survey: First Update EPA 560/13-79-018, December 1980.

Forty-nine halogenated hydrocarbons (HHC) were selected for the first metabolism review based on the following information:

1. halocarbons occurring in air, water, food, biological fluids, and tissues;

2. halocarbon production, usage, and disposal facilities in the selected study areas; and

3. halocarbon mutagenicity and carcinogenicity data.

Details of HHC selection process are included in the report Formulation of A Preliminary Assessment of Halogenated Organic Compounds in Man and Environmental Media EPA 560/13-79-006, July 1979.

The first literature survey provided metabolism summaries as well as basic information on the physical properties of the 30 HHC's reviewed. The first update report updated information on 15 of the original HHC's plus provided physical data and metabolism summaries for 4 additional HHC's not included in the first survey. This second update provides information on 23 HHC's found in the literature from January 1978 through November 1980.

Basic information on the physical properties of the compounds at the beginning of each summary includes molecular and structural formulas, the Chemical Abstracts Service Registry number (CAS RN), accepted synonyms (syn), molecular weight (mol wt), boiling point (bp), and vapor pressure (vp). The

text summarizes the available information on the uptake and retention of the compound, its subsequent distribution and elimination patterns, the identification and observed concentrations of metabolites, and the metabolic pathways involved.

The basis of this second update reflects a more extensive search strategy than did the first update. The databases were updated from 1978 and include the following:

Agricola

Biosis

Chemical Abstracts

Commonwealth Agricultural Bureau Abstracts

Comprehensive Dissertation Abstracts

Conference Papers Index

Enviroline

Environmental Periodicals Bibliography

Excerpta Medica

IRL Life Sciences

Medline

National Technical Information Service

Pollution Asbtracts

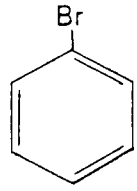
Scisearch

Toxline

METABOLISM SUMMARIES

BROMOBENZENE

C_6H_5Br



CAS: 000108861

Syn: phenyl bromide

Mol wt: 157.02 g/mol

bp: 156°C (at 760 mm Hg)

vp: 4.3 mm Hg (at 25°C)

The in vitro pathway of bromobenzene enzymatic activation to either bromobenzene 3,4-epoxide or bromobenzene 2,3-epoxide is by hepatic cytochrome P-450 as shown in Figure 1. Metabolite formation in rat liver microsomes is proportional to the enzyme concentration and is markedly changed after pretreatment with various inducers (Lau and Zannoni, 1979; Zannoni and Lau, 1979). The amount of metabolite produced is dependent upon the inducer: phenobarbital induces both the o- and p-bromophenol pathway while 3-methylcholanthrene or beta-naphthoflavone markedly induces the o-bromophenol pathway. Discontinuous polyacrylamide gel electrophoresis was used to correlate the relative activity of the 3,4-epoxide and 2,3-epoxide pathways with various molecular forms of cytochrome P-450. Multiple bands in the 40,000 to 60,000 molecular weight range showed significant differences depending upon the inducer. The two pathways of bromobenzene metabolism each preferentially require different forms of cytochrome P-450.

Wiley et al. (1979) measured the in vitro disappearance of 1 mM tritium-labelled bromobenzene from rat liver microsomes (8-12 mg) to be 0.864 nmol/mg protein/min. At substrate concentrations greater than 0.3 nmol, the reaction velocity markedly increases, suggesting multi-enzyme metabolism. Phenobarbital induced a 9-fold increase in bromobenzene covalent binding to microsomal protein. Covalent binding is completely inhibited by 0.1 mM glutathione, which is due to competition for the arene oxides by the glutathione transferase reactions.

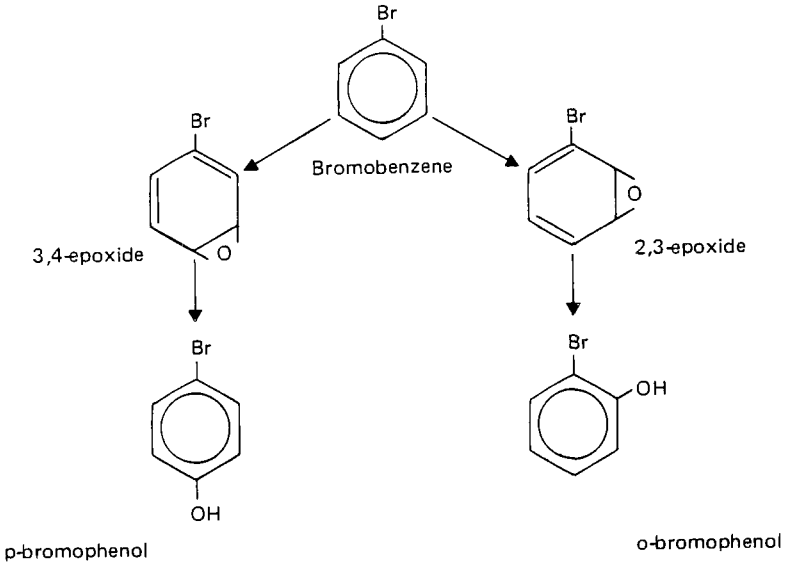


Fig. 1. Bromobenzene metabolism.

Reprinted from: Hepatic microsomal epoxidation of bromobenzene to phenols and its toxicological implication. Toxicology and Applied Pharmacology, 50:309-318, 1979 by Serrine S. Lau and Vincent G. Zannoni with permission of Academic Press, Inc.

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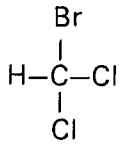
Zannoni VG, Lau SS. 1979. Hepatic microsomal epoxidation of bromobenzene to phenols and its toxicological implication. Toxicol. Appl. Pharmacol. 50(2):309-318.

BROMODICHLOROMETHANE

$CHBrCl_2$



CAS: 000075274

Syn: bromodichloromethane; dichlorobromomethane; monobromodichloromethane

Mol wt: 163.8 g/mol

bp: 90°C (at 760 mm Hg)

Bromodichloromethane metabolism to carbon monoxide in rat liver microsomes was studied by Ahmed et al. (1977). Bromodichloromethane (26 mM) incubated with hepatic microsomes (2.4-3.0 mg protein) resulted in a carbon monoxide formation rate of 0.04 nmol/mg/min (enzymatic: 37°C for 15 minutes). This was a relatively low rate when compared to other halomethanes but was three times the control rate observed with boiled microsomes. Anders et al. (1978) did not find elevated blood carbon monoxide levels after administering a single 1 mmol/kg intraperitoneal dose of bromodichloromethane.

Pfaffenberger et al. (1979) measured the distribution of bromodichloromethane between rat blood serum and adipose tissue by a gas-liquid chromatography procedure. Rats dosed for 25 days with bromodichloromethane showed tissue storage but these levels did not increase with time. Average values for adipose (hexane extracted) and serum bromodichloromethane concentrations were 51 ppb and 1 ppb, respectively, for the 0.5 mg/day dose group. Increased levels of 1800 ppb (adipose) and 23 ppb (serum) were noted for the 5.0 mg/day dose groups. Three to 6 days after cessation of dosing, adipose levels decreased rapidly to 4 ppb for the 0.5 mg/day dose group and to 3 ppb for the 5.0 mg/day dose group. Serum levels in both groups dropped to 1 ppb.

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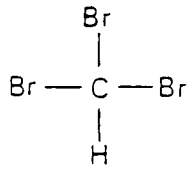
Ahmed AE, Kubic VL, Anders, MW. 1977. Metabolism of haloforms to carbon monoxide. I. In vitro studies. Drug Metab. Dispos. (U.S.A.) 5(2):198-204.

Anders MW, Stevens JL, Sprague RW, Shaath Z, Ahmed, AE. 1978. Metabolism of haloforms to carbon monoxide. II. In vitro studies. Drug Metab. Dispos. 6(5):556-560.

Pfaffenberger CD, Peoples AJ, Enos HF. 1979. Distribution study of volatile halogenated organic compounds between rat blood serum and adipose tissue using a purge/trap procedure. Adv. Chromatogr. 14:639-652.

BROMOFORM

$CHBr_3$



CAS: 000075252

Syn: tribromomethane; methenyl tribromide

Mol wt: 252.75 g/mol

bp: 149.5°C (at 760 mm Hg)

vp: 6.11 mm Hg (at 25°C)

Stevens and Anders (1979) studied the in vitro biotransformation of bromoform to carbon monoxide (CO) by the microsomal mixed function cytochrome P-450 oxygenase system involving glutathione (GSH) and proposed the following metabolic pathway: $CHBr_3 \rightarrow COHBr_3 \rightarrow Br_2CO$; $Br_2CO + GSH \rightarrow GS(C{=}O)Br$; $GS(C{=}O)Br + GSH \rightarrow GSSG + (:C{=}O)$

Microsomal incubation with either $^{13}CHBr_3$ or $^{18}O_2$ confirmed that the sources of carbon and oxygen in released carbon monoxide are bromoform and molecular oxygen, respectively, as shown by Ahmed et al. (1977). Two moles of glutathione disappear during the formation of 1 mole of carbon monoxide and 1 mole of oxidized glutathione (GSSG). Carbon monoxide formation is 1.23 nmol/mg/min for the microsomes. The addition of glutathione to an NADPH incubation mixture increases carbon monoxide formation as much as 8-fold implying a direct involvement in the reactions. Phenobarbital or 3-methylcholanthrene pretreatment increases the carbon monoxide formation rate by 75% or 60% respectively, while cobaltous chloride treatment decreases and SKF-525-A treatment inhibits carbon monoxide formation.

Anders et al. (1978) studied the in vivo bromoform metabolism in rats by intraperitoneal administration of 1, 2, or 4 mmol/kg doses. Increasing bromoform concentration resulted in increasing levels of carbon monoxide in the blood. Phenobarbital pretreatment markedly increased blood carbon monoxide levels while SKF-525-A lowered blood carbon monoxide levels following bromoform injection. 3-Methylcholanthrene pretreatment did not increase the blood levels.

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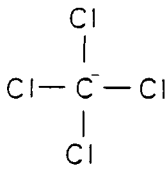
Stevens JL, Anders, MW. 1979. Metabolism of haloforms to carbon monoxide. III. Studies on the mechanism of the reaction. Biochem. Pharmacol. 28(21):3189-3194.

CARBON TETRACHLORIDE

CCl_4



CAS: 000056235

Syn: methane tetrachloride; tetrachloromethane; perchloromethane

Mol wt: 153.82 g/mol

bp: 76.54°C (at 760 mm Hg)

vp: 98.9 mm Hg (at 25°C)

Carbon tetrachloride appears to be metabolized to phosgene and carbon dioxide through biotransformation via the heme system and cytochrome P-450, as demonstrated by Mansuy et al. (1980) and Shah et al. (1979).

Mansuy et al. (1980) propose that carbon tetrachloride converts primarily to phosgene from a reaction of dioxygen either with intermediate $FeCCl_3$ or $FeCCl_2$ carbene complexes, depending on the nature of the reducing agent. It is suggested that phosgene could react with nucleophilic groups (NuH) of cell macromolecules producing unstable Nu-COCl intermediates which then could react with an additional nucleophilic group to create stable covalent adducts. This proposed pathway, as shown in Figure 1, yields carbon dioxide as the main stable metabolite of carbon tetrachloride metabolism.

The metabolism of carbon tetrachloride was studied by Shah et al. (1979) to investigate the mechanism of its carcinogenicity. Liver homogenates from male rats were incubated with labelled carbon tetrachloride and NADH or NADPH in the presence or absence of carbon tetrachloride metabolites or substrates for reaction with carbon tetrachloride metabolites. The conversion of carbon tetrachloride to carbon dioxide as well as its binding to lipid and protein were observed after incubation with NADPH. The formation of 2-oxothiazolidine-4-carboxylic acid demonstrates the metabolic formation of phosgene from carbon tetrachloride.

Pfaffenberger et al. (1979) using gas-liquid chromatography studied the distribution of carbon tetrachloride between rat blood serum and adipose tissue. Blood and adipose tissue were collected and analyzed from rats gavaged for 25 days with 1 or 10 mg carbon tetrachloride. On day 25, the blood serum carbon tetrachloride levels averaged 11 ppb and the fat carbon tetrachloride levels averaged 1.9 ppm for the 10-mg dosed rats. The metabolite chloroform was detected in the blood serum (59 ppb) and fat (2.62 ppm) in the 10-mg dosed rats. Following cessation of dosing, levels dropped roughly 10-fold.

Statham et al. (1978) studied the uptake, elimination, distribution, and toxic effects of carbon tetrachloride in rainbow trout. Uptake was determined by exposing 15 trout to labelled carbon tetrachloride for 0 to 1.5 hours at a dose of 1 mg/liter in water. Fat, liver, blood, and muscle all showed carbon tetrachloride uptake. During exposure, fat levels steadily increased to near 1 nmol/g while liver, blood, and muscle peaked between 15 to 30 minutes and then steadily declined. Following 2 hours of exposure, blood, bile, liver, heart, muscle, gill, brain, skin, and spleen all showed decreasing levels through 8 hours. Fat levels continued to rise through the second hour following cessation of exposure.

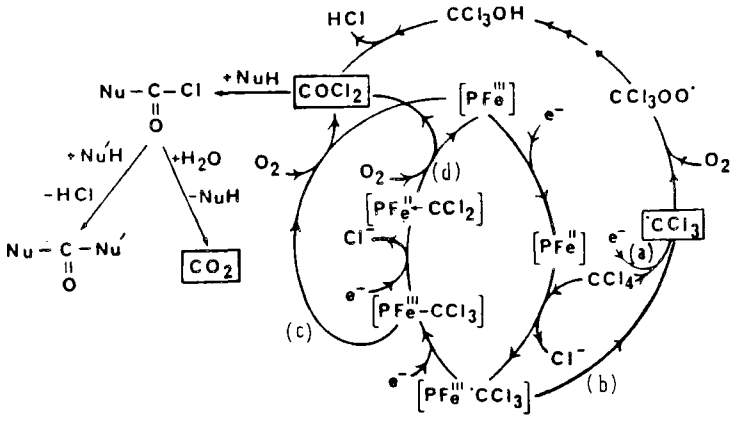
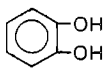


Fig. 1: Proposed mechanism for CCl_4 biotransformation by the heme system and cytochrome P450 (P=TPP or cytochrome P450; NuH and Nu'H =  **or nucleophilic groups of microsomal proteins).**

Reprinted from: A heme model study of carbon tetrachloride metabolism: mechanisms of phosgene and carbon dioxide formation. Biochemical and Biophysical Research Communications, 95:1536-1542, 1980 by D. Mansuy, M. Fontecave and J. C. Chottard with permission of Academic Press, Inc.

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Pfaffenberger CD, Peoples AJ, Enos HF. 1979. Distribution study of volatile halogenated organic compounds between rat blood serum and adipose tissue using a purge/trap procedure. Adv. Chromatogr. 14:639-652.

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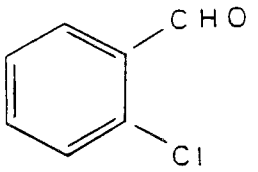
CHLOROBENZALDEHYDE

C_7H_5ClO



CAS: 000089985

Syn: 2-chlorobenzaldehyde; ortho-chlorobenzaldehyde

Mol wt: 140.57 g/mol

bp: 211.9°C (at 760 mm Hg)

vp: 1.07 mm Hg (at 25°C)

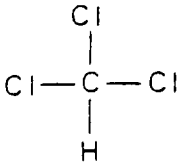
A study of chlorobenzaldehyde as a metabolite of o-chlorobenzylidene malononitrile was presented by Paradowski (1979). Toxic doses of o-chlorobenzylidene malononitrile were intravenously administered to rabbits and the following metabolic pathway determined. o-Chlorobenzylidene malononitrile biotransformation occurred mainly in the blood by two independent pathways: rapid hydrolysis to o-chlorobenzaldehyde and malononitrile as the dominant reaction (30%-40% of o-chlorobenzylidene malononitrile) or reduction to o-chlorobenzyl malononitrile (10% of o-chlorobenzylidene), while the remaining 50%-60% of the o-chlorobenzylidene malononitrile administered disappeared from blood by other pathways. o-Chlorobenzaldehyde was about twice as toxic (average LD_{50} = 8.5 mg/kg) as o-chlorobenzylidene malononitrile (average LD_{50} = 18.3 mg/kg). Exclusion of the liver from the circulatory path increased the amount of o-chlorobenzaldehyde produced to 75% of administered o-chlorobenzylidene malononitrile with about 15% of the o-chlorobenzylidene malononitrile being reduced to o-chlorobenzyl malononitrile. Renal exclusion from circulation followed by o-chlorobenzylidene malononitrile dosing did not alter its biotransformation in blood. The in vitro metabolism of o-benzylidene malononitrile was quantitatively different from its in vivo metabolism, with considerably slower reaction rates of formation and elimination of metabolites in blood. The toxic activity of o-chlorobenzylidene malononitrile was due to its metabolism to the more toxic o-chlorobenzaldehyde. o-Chlorobenzylidene malononitrile reduction to the benzyl malononitrile demonstrated a minor detoxication pathway.

REFERENCE

Paradowski M. 1979. Metabolism of toxic doses of o-chlorobenzylidene malononitrile in rabbits. Pol. J. Pharmacol. Pharm. 31(6):563-572.

CHLOROFORM

$CHCl_3$



CAS: 000067663

Syn: formyl trichloride; methane trichloride; methynyl trichloride; methyl trichloride; trichloroform; trichloromethane

Mol wt: 119.38 g/mol

bp: 61.7°C (at 760 mm Hg)

vp: 173.1 mm Hg (at 25°C)

Chloroform is reported to be metabolized in phenobarbital-treated animals to phosgene, which reacts with cysteine to form 2-oxothiazolidine-4-carboxylic acid. Carbon dioxide is the final metabolic product (Ahmed et al., 1980; Mansuy, 1977; Pohl et al., 1977; Pohl et al., 1978; Pohl et al., 1979).

Mansuy (1977) studied the in vitro metabolism of chloroform to a reactive metabolite. Adult male rats were pretreated with 80 mg/kg phenobarbital each day for 3 days prior to sacrifice. Liver microsomal suspensions were incubated for 15 minutes with or without cysteine. Phosgene appeared to be the reactive metabolite, and could be hydrolyzed to carbon dioxide or trapped with cysteine to form 4-carboxy-thiazolidine-2-one.

Pohl et al. (1977) also studied the metabolism of chloroform to phosgene by liver microsomes. Male rats, pretreated with phenobarbital 1, 2, and 3 days before dosing, were sacrificed and these liver microsomal proteins were incubated with 1.00 mmol labelled chloroform. Chloroform was hydroxylated to trichloromethanol by cytochrome P-450 monoxygenases. The alcohol then underwent spontaneous dehydrochlorination to form phosgene which could react with excess cysteine or microsomal proteins.

Pohl and Krishna (1978) continued their earlier work to investigate the in vitro metabolism of chloroform to a reactive metabolite. Male rats were pretreated with phenobarbital 1, 2, and 3 days prior to preparation of microsomes. Following incubation of 1 nmol chloroform at 37°C for 10 minutes with microsomes, approximately 2 nmol of phosgene appeared as the major metabolite and was trapped with cysteine forming 2-oxathiazolidine-4-carboxylic acid. Pohl et al. (1979) continued their studies to show phosgene as a possible hepatotoxic metabolite of chloroform.

Kluwe (1979) investigated the covalent binding of chloroform metabolites in the liver and kidney. Labelled chloroform was administered in a 1.75 mmol/kg dose to male mice. The mice were sacrificed 3 hours after

administration and subcellular fractions were prepared from liver and kidney. Covalent binding of the radioactivity to subcellular fractions was variable, with the highest levels observed in liver cytosol and kidney mitochondria, the lowest in liver mitochrondria and kidney cytosol. It is suggested that the chloroform metabolite covalently bound to the liver and kidney is not the same metabolite that causes hepatic and renal injury.

Ahmed et al. (1980) have summarized the metabolism studies on chloroform. Chloroform is metabolized *in vivo* and *in vitro* to carbon dioxide. Phenobarbital and 3-methylcholanthrene pretreatments increased the metabolic rate and hepatotoxic effects. Phosgene appeared as an intermediate and reacted with cysteine forming 2-oxothiazolidine-4-carboxylic acid. Covalent binding of chloroform to hepatic proteins and lipids may be attributed to the highly reactive phosgene metabolite which can acylate tissue nucleophiles and crosslink macromolecules.

In a study to determine if carbon monoxide was a metabolite of chloroform, Ahmed et al. (1977) studied the *in vitro* metabolism of chloroform. Hepatic fractions from 3-methylcholanthrene- or phenobarbital-treated rats were incubated with 60 umol of chloroform. Nonenzymatic rates of carbon monoxide formation were determined by heating the reaction mixture for 4 minutes at 100°C. The microsomal conversion of chloroform to carbon monoxide was 0.03 nmol/mg/min for enzymatic incubations and 0.00 nmol/mg/min for nonenzymatic reactions.

Anders et al. (1978) studied the metabolism of chloroform to carbon monoxide. Male rats received a single 1 mmol/kg intraperitoneal dose of chloroform and blood carbon monoxide levels were measured for 4 hours at 1 hour intervals. The administration of chloroform did not increase blood carbon monoxide levels.

Pfaffenberger et al. (1979) studied the distribution of chloroform between rat blood serum and adipose tissue using a purge/trap/desorb-gas-liquid chromatography procedure. Rats were administered varied doses of chloroform followed by collection and analysis of blood and adipose tissue samples. Increased levels of chloroform appeared in the blood and adipose tissue within 2 hours after dosing. In the first experiment, eight rats were administered 40 mg of chloroform by gavage for 2 consecutive days. Two rats were killed 2 hours after the second dose and the level of chloroform in the fat was between 3 and 15 ppm. Rats killed 26 hours after dosing had chloroform levels in fat approximately equal to levels in controls. In a second study, ten rats received 5 mg of chloroform by gavage and killed 2 hours after dosing. Chloroform levels of 20 ppm in the fat and 18 ppb in the serum were detected.

Vogt et al. (1979) investigated the formation of chloroform *in vivo* and *in vitro*. Sprague-Dawley rats were fasted for 15 hours prior to intragastric intubation of sodium hypochlorite containing 20-80 mg chlorine. Tissue homogenates were incubated with sodium hypochlorite *in vitro*. Chloroform levels were highest 1.5 hours after intubation and were almost completely eliminated after 24 hours. Increased doses of sodium hypochlorite resulted in greater chloroform formation both *in vitro* and *in vivo*, with the highest levels occurring in the blood and fat.

Withey and Collins (1980) studied the pharmacokinetics of chloroform metabolism in male Wistar rats. Varied doses (3, 6, 9, 12, or 15 mg/kg) of chloroform were administered intravenously and blood samples were collected at selected time intervals. Tissue samples yielded meaningful kinetic data only at the highest dose level (15 mg/kg).

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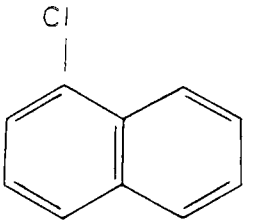
CHLORONAPHTHALENE

$C_{10}H_7Cl$

Mol wt: 162.62 g/mol

1-chloronaphthalene



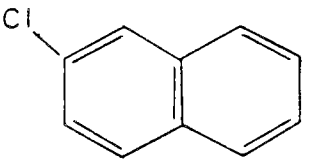
CAS: 000090131

Syn: alpha-chloronaphthalene; alpha-chlornaphthalene

bp: 258.8°C (at 753 mm Hg); 106.5°C (at 5 mm Hg)

vp: 1.36 mm Hg (at 80.6°C)

2-chloronaphthalane



CAS: 000091587

Syn: beta-chloronaphthalene

b.p.: 256°C (at 760 mm Hg)

Ruzo et al. (1976) studied the concentrations of 1- or 2-chloronaphthalene substrates and their metabolites during the first 6 hours after retrocarotid injection (300 mg) in blood and after 6 hours in blood, urine, bile, and organ samples from two female Yorkshire pigs. The 1-chloronaphthalene concentration was 5.1 ug/g in blood 10 minutes after injection and decreased with time. Its metabolite, 4-chloronaphthol, was first detected in blood after 160 minutes and increased with time. 2-Chloronaphthalene concentrations were similar to those observed for the 1-chloro isomer. 3-Chloro-2-naphthol, the major metabolite of 2-chloronaphthalene, was first detected in the blood after 200 minutes and increased with time. The chloroisomer substrates 6 hours after injection were distributed primarily in the brain (6.7 ug/g 1-Cl; 21.4 ug/g 2-Cl) and kidney (16.1 ug/g 1-Cl; 14.4 ug/g 2-Cl). The fat tissue concentrations were low (0.6 ug/g 2-Cl) indicating that these lipophilic substrates were not concentrated during the first 6 hours. Metabolites were identified in the kidney tissues (1.4 ug/g 4-Cl; 0.6 ug/g 3-Cl-2-Naph.), liver tissues (1.0 ug/g 4-Cl; 0.7 ug/g 3-Cl-2-Naph.), urine (440 ug/g 2-Cl; 60 ug/g 3-Cl-2-Naph.) and bile (900 ug/g 2-Cl; 260 ug/g 3-Cl-2-Naph.). Chloronaphthalenes were rapidly metabolized, most probably by the liver which possesses oxidative enzymes.

Secours et al. (1977) administered a single oral dose of various dichloronaphthalenes (400 mg/kg) to male rats and identified urinary metabolites. 1,2-Dichloronaphthalene yielded the glucuronide conjugate of 5,6-dichloro-1,2-dihydroxy-1,2-dihydronaphthalene; 2,7-dichloronaphthalene was

metabolized to free and conjugated 7-chloro-2-naphthol; and 2,6-dichloronaphthalene yielded free and conjugated 6-chloro-2-naphthol and 2,6-dichloronaphthol.

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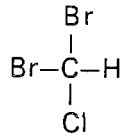
Secours V, Chu I, Viau A, Villeneuve DC. 1977. Metabolism of chloronaphthalenes. J. Agric. Food Chem. 25(4):881.

DIBROMOCHLOROMETHANE

$CHBr_2Cl$



CAS: 000124481

Syn: chlorodibromomethane; dibromochloromethane; dibromomonochloromethane; monochlorodibromomethane

Mol wt: 208.3 g/mol

bp: 119-120°C (at 748 mm Hg)

The in vitro metabolism of dibromochloromethane to carbon monoxide in rats was investigated by Ahmed et al. (1977). Hepatic microsomes containing 2.4-3.0 mg protein were incubated with 26 mM dibromochloromethane at 37°C for 15 minutes. The microsomal conversion of dibromochloromethane to carbon monoxide was 0.42 nmol/mg/min for enzymatic incubations and 0.03 nmol/mg/min for the nonenzymatic rate.

Anders et al. (1978) measured in vitro metabolism of dibromochloromethane to carbon monoxide. After rats received a single 1 mmol/kg intraperitoneal injection of dibromochloromethane, blood carbon monoxide levels increased (see Figure 1).

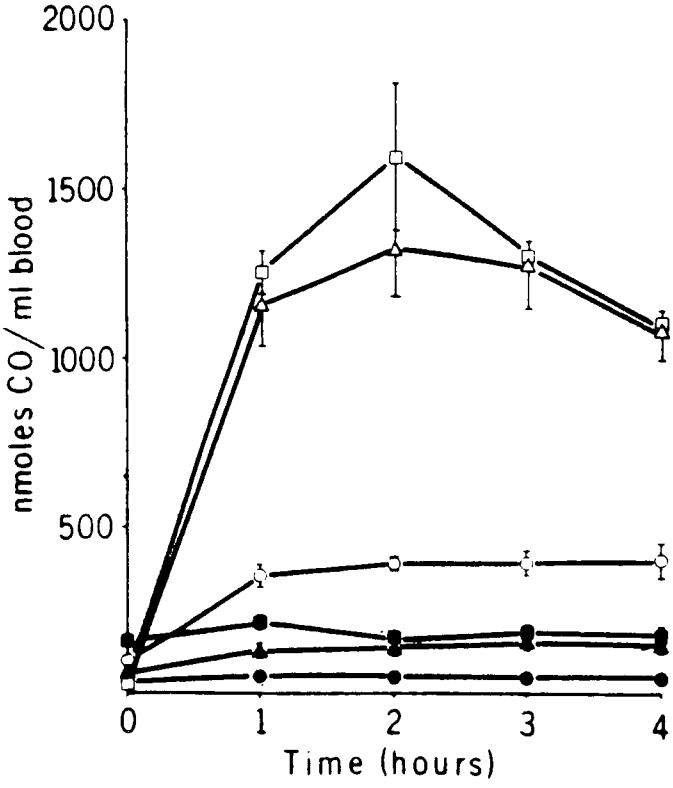


Fig. 1. Blood carbon monoxide levels after the administration of bromoform, chloroform, dibromochloromethane, dichlorobromomethane, or iodoform. Control (●), dichlorobromomethane (▲), chloroform (■), dibromochloromethane (○), bromoform (△), and iodoform (□).

Reprinted from: Metabolism of haloforms to carbon monoxide. II. In vivo studies. Drug Metabolism and Disposition, 6(5):556-560, 1978 by M.W. Anders, J.L. Stevens, R.W. Sprague, Z. Shaath, and A.E. Ahmed with permission of The Williams and Wilkens Company.

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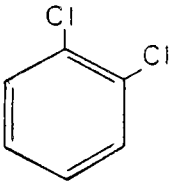
Anders MW, Stevens JL, Sprague RW, Shaath Z, Ahmed A.E. 1978. Metabolism of haloforms to carbon monoxide. II. In vitro studies. Drug Metab. Dispos. 6(5):556-560.

DICHLOROBENZENE

$C_6H_4Cl_2$

Mol wt: 147.01 g/mol

ortho-dichlorobenzene



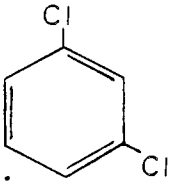
CAS: 000095501

Syn: o-dichlorobenzene; 1,2-dichlorobenzene; ODB; ODCB; orthodichlorobenzene; orthodichlorobenzol

bp: 180.5°C (at 760 mm Hg)

vp: 1.5 mm Hg (at 25°C)

meta-dichlorobenzene



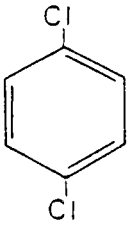
CAS: 000541731

Syn: m-dichlorobenzene; 1,3-dichlorobenzene; metadichlorobenzene; metadichlorobenzol

bp: 173°C (at 760 mm Hg)

vp: 2.3 mm Hg (at 25°C)

para-dichlorobenzene



CAS: 000106467

Syn: p-dichlorobenzene; paradichlorobenzene; paradichlorobenzol

bp: 174°C (at 760 mm Hg)

vp: 1.1 mm Hg (at 30.0°C)

No pertinent literature was available on ortho- or meta-dichlorobenzene during the search period.

p-Dichlorobenzene, a volatile environmental contaminant, was found in human fat, pigeon fat, and ambient air (Tokyo, Japan) by Morita et al. (1978) in concentrations of 1.88 ± 2.13 ppm; 1.85 ± 0.75 ppm; and 2.63 ± 0.32 ppm, respectively. Less variation was found in pigeon fat concentrations due to their exposure to nearly constant ambient air concentrations, whereas variations in human fat reflected the diversity of physical exposure times and concentrations of p-dichlorobenzene. The chemical is used primarily as a moth

repellent and reaches concentrations of several hundred ug/m^3 in indoor air. No p-dichlorobenzene was detected in water, fish, dairy products, and cereals.

Hawkins et al. (1980) studied ^{14}C-p-dichlorobenzene metabolism in rats by three administration routes: oral (250 mg/kg/day), subcutaneous (250 mg/kg/day), and inhalation (1000 ppm for 3 hr/day). Inhalation and oral routes displayed similar distribution and excretion patterns. Tissue levels were highest in liver and kidney. Subcutaneous dosing produced lower peak concentrations but maintained steady state levels for a longer period. Fat tissue had the highest p-dichlorobenzene tissue concentration. Each route

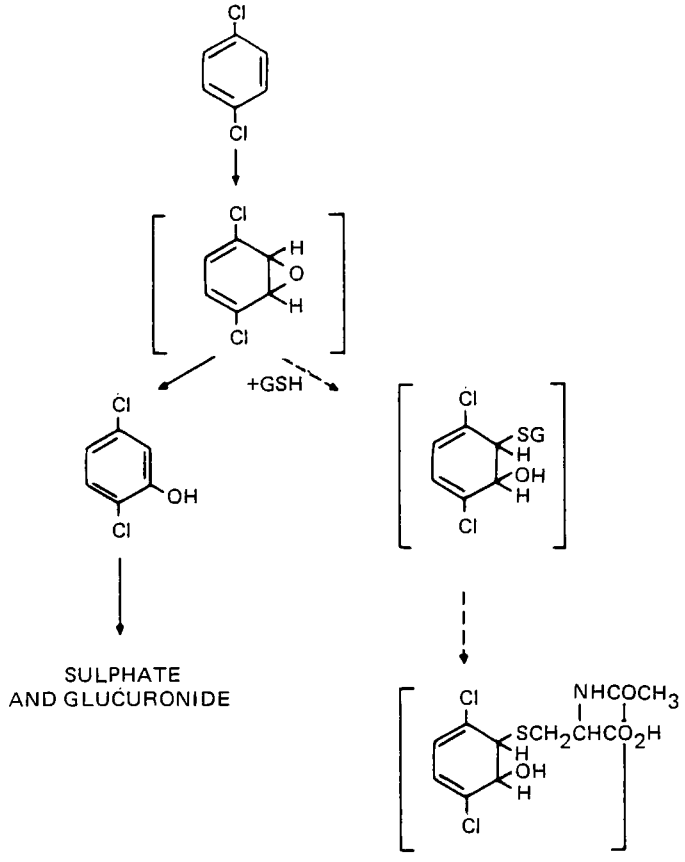


Fig. 1. Postulated biotransformation pathway of p-dichlorobenzene in rats.

Reprinted from: The distribution, excretion and biotransformation of p-dichloro(^{14}C)benzene in rats after repeated inhalation, oral and subcutaneous doses. Xenobiotica 10(2):81-95, 1980 by D.R. Hawkins, L.F. Chasseaud, R.N. Woodhouse and D.G. Cresswell with permission of Taylor and Francis, Ltd.

produced p-dichlorobenzene tissue concentrations after repeated dosing, with rapid decline in all tissues and extremely low level detection in fat only 5 days after dosing. p-Dichlorobenzene was rapidly absorbed and cleared from the lungs. Clearance from fat tissue was slower but by 120 hours had decreased nearly 500 times. A proposed metabolic pathway in rats is shown in Figure 1. Between 90%-97% of the eliminated doses appeared in urine within 5 days regardless of the route. Approximately 50%-60% of the eliminated dose was excreted in the bile within 48 hours but most was reabsorbed and eliminated in urine. The major urinary metabolites were the sulfate (46%-54%) and glucuronide conjugates (31%-34%) of 2,5-dichlorophenol. A dihydroxydichlorobenzene conjugate (possibly 2,5-dichloroquinol) and mercapturic acid were also identified as minor urinary components after acid hydrolysis. There were some quantitative differences in urinary metabolites depending upon the dosage route but larger variations were noted in the distribution of metabolites from bile. A major biliary metabolite was 2,5-dichlorophenol glucuronide (30%-42%). A second major component not identified was assumed to be reabsorbed and further metabolized before elimination in urine.

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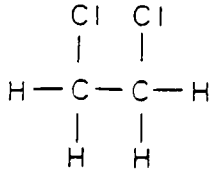
Morita M, Ohi G. 1978. p-Dichlorobenzene in pigeon and human adipose tissue. Chemosphere 7(10):839-842.

1,2-DICHLOROETHANE

$C_2H_4Cl_2$



CAS: 000107062

Syn: sym-dichloroethane; alpha,beta-dichloroethane; dichloroethylene; EDC; ethane dichloride; ethylene chloride; ethylene dichloride; glycol dichloride

Mol wt: 98.96 g/mol

bp: 83.47°C (at 760 mm Hg)

vp: 76.2 mm Hg (at 25°C)

Kokarovsteva et al. (1978) identified chloroethanol in the blood and liver of rats after a single oral 750 mg/kg dose of 1,2-dichloroethane. In blood, the chloroethanol concentration was 5.6 ug/ml after 1 hour, peaking at 4 hours (67.8 ug/ml) and declining through 12 hours (37.6 ug/ml), 24 hours (14.1 ug/ml), and 48 hours (8.2 ug/ml). In the liver, chloroethanol was not found after 1 and 4 hours, but was detected after 12 hours (0.5 ug/g), 24 hours (13.5 ug/g); the concentration slowly decreased through 48 hours (13.0 ug/g). Chloroethanol was highly toxic (LD_{50} = 87 mg/kg) and was rapidly absorbed into blood and metabolized within 24 hours to monochloroacetic acid.

Livesey et al. (1979) investigated an alternate pathway of 1,2-dichloroethane metabolism to ethylene in vitro involving conjugation with glutathione (see Figure 1). Various rat tissue cytosol fractions incubated with 255 umol 1,2-dichloroethane showed linear ethylene production rates for at least 1 hour: liver (10.3 pmol/min/mg), kidney (5.2 pmol/min/mg), and lung (0.8 pmol/min/mg). No activity was observed in muscle. Metabolic inhibitors such as cyanide, fluoride, SKF-525-A, and EDTA had no inhibitory effect. p-Chloromercuribenzoic acid, diethyl maleate, or methyl iodide (substrates for GSH-S transferases) markedly inhibited ethylene production.

Withey et al. (1980) studied the pharmacodynamics of 1,2-dichloroethane in rats by intravenous administration of 3, 6, 9, 12, or 15 mg/kg. 1,2-Dichloroethane was rapidly eliminated from the blood and tissue. Tissue samples yielded meaningful kinetic data at only the highest dose level (15 mg/kg); elimination was essentially complete after 300 minutes except in perirenal fat. 1,2-Dichloroethane uptake/elimination in fat is described by a one compartment model: time for maximal accumulation = 32.5 minutes, peak concentration = 24.92 ug/g, and elimination half-life = 78 minutes.

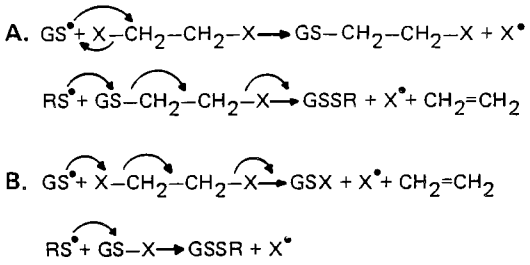


Figure 1. Possible reaction mechanisms for the conversion of 1,2-dihaloethanes to ethylene.

Reprinted from: In vitro metabolism of 1,2-dihaloethanes to ethylene. Drug Metabolism and Disposition, 7:199-203, 1979 by J.C. Livesey and M.W. Anders with permission of the Williams and Wilkins Company.

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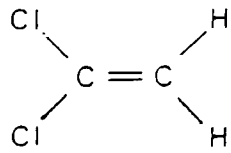
Livesey JC, Anders MW. 1979. In vitro metabolism of 1,2-dihaloethanes to ethylene. Drug Metab. Dispos. 7(4):199-203.

Withey JR, Collins BT. 1980. Chlorinated aliphatic hydrocarbons used in the foods industry: the comparative pharmacokinetics of methylene chloride, 1,2-dichloroethane, chloroform and trichloroethylene after i.v. administration in the rat. J. Environ. Pathol. Toxicol. 3(5-6):313-332.

1,1-DICHLOROETHYLENE

$C_2H_2Cl_2$



CAS: 000075354

Syn: 1,1-DCE; 1,1-dichloroethene; vinylidene chloride; vinylidine chloride

Mol wt: 96.94 g/mol

bp: 37°C (at 760 mm Hg)

vp: 633.7 mm Hg (at 25°C)

The major metabolites of 1,1-dichloroethylene have been reported to be thiodiglycolic acid, S-(carboxymethyl)-N-acetylcysteine, and methylthio-acetylaminoethanol by Reichert (1979) and Reichert et al. (1979). Jaeger (1977) proposed that 1,1-dichloroethylene is metabolized to monochlorocitric acid. Jones and Hathway (1977) suggest thiodiglycolic acid and an N-acetyl-S-cysteinyl-acetyl derivative as the major urinary metabolites with substantial levels of chloroacetic acid, dithioglycolic acid, and thioglycolic acid.

Jaeger (1977) studied the inhibition of hepatic mitochondrial metabolism in fasted rats exposed to 1,1-dichloroethylene. Male rats received a single 250 ppm inhalation exposure to 1,1-dichloroethylene and selected tests on isolated mitochondria were conducted for 1 to 24 hours after exposure. 1,1-Dichloroethylene toxicity appeared to result from mitochondrial injury. The author proposed that 1,1-dichloroethylene is metabolized via monochloroacetic acid to monochlorocitric acid which may inhibit aconitase and block citrate oxidation in the mitochondria.

The metabolism of 1,1-dichloroethylene in adult male rats was investigated by Jones and Hathway (1977). Doses of 500 ug/kg or 350 mg/kg of labelled 1,1-dichloroethylene were administered via gavage, intravenous, or intraperitoneal routes for 72 hours. Almost all radioactivity was recovered during the first 72 hours after dosing. Most of the 1,1-dichloroethylene was eliminated via the lungs. As shown in Figure 1, 1,1-dichloroethylene could be metabolized primarily to thiodiglycolic acid and an N-acetyl-S-cysteinyl-acetyl derivative and excreted by the kidneys although significant levels of chloroacetic acid, dithioglycolic acid, and thioglycolic acid were present.

Reichert and Werner (1978) studied the metabolic fate of labelled 1,1-dichloroethylene by administering a single oral dose (0.5, 5.0, or 50 mg/kg) to rats. The urine and feces were collected for 72 hours after administration and analyzed. At the 0.5 mg/kg dose, 0.9% of the

1,1-dichloroethylene was expired unchanged, 23% was expired as (^{14}C) carbon dioxide, and 52% was excreted unchanged via the urine. The major metabolite was thiodiglycolic acid. In a 1979 abstract, Reichert identified three major metabolites of 1,1-dichloroethylene as thiodiglycolic acid, S-(carboxymethyl)-N-acetylcysteine, and methylthioacetylaminoethanol.

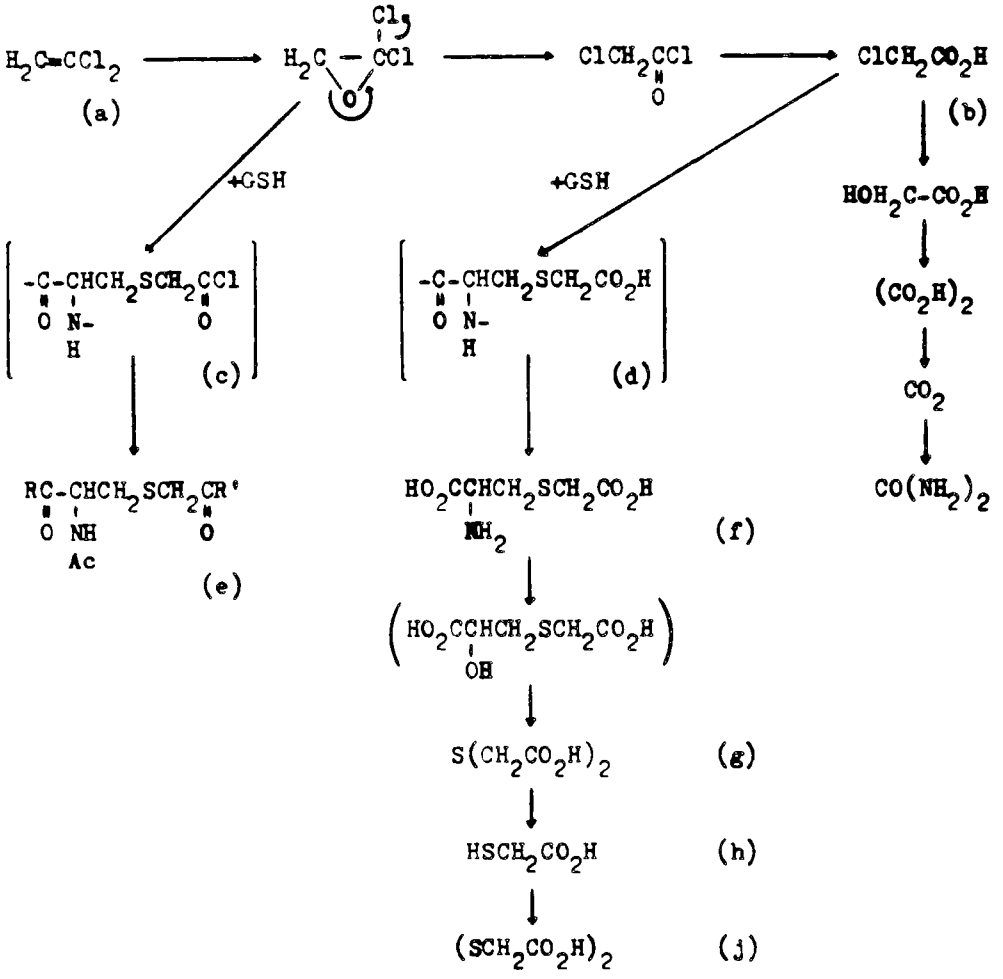


Fig. 1. Scheme for the metabolism of 1,1-dichloroethylene in rats.

Reprinted from: The biological fate of vinylidene chloride in rats. Chemico-Biological Interactions, 20:27-41, 1978 by B.K. Jones and D.E. Hathway with permission of Elsevier/North Holland Scientific Publishers, Ltd.

A follow-up study by Reichert et al. (1979) showed that a single oral dose of 0.5, 5.0, or 50 mg/kg of labelled 1,1-dichloroethylene was metabolized in rats to the three metabolites mentioned above. After 72 hours, 1.26%, 9.70%, and 16.47%, respectively, of the total radioactivity was exhaled unchanged and

13.64%, 11.35%, and 6.13%, respectively, was exhaled as (^{14}C) carbon dioxide. The main portion of the radioactivity was recovered from the urine (43.55%, 53.88%, and 42.11%, respectively, for the three metabolites), implying that the metabolic pathway is saturable. The amount of radioactivity eliminated in the feces was 15.74%, 14.54%, and 7.65%, respectively. The metabolic pathway is shown in Figure 2.

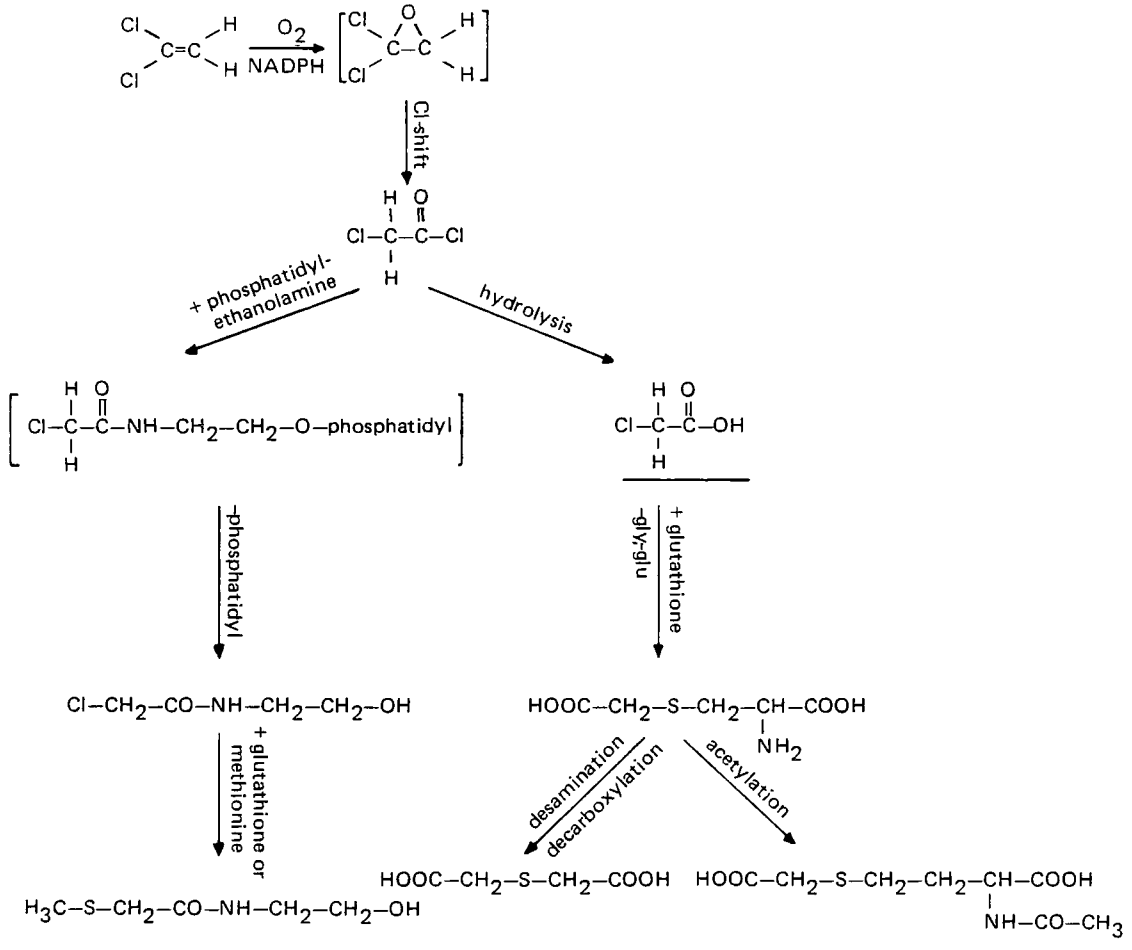


Fig. 2. Metabolic pathways of 1,1-dichloroethylene. Identified metabolites underlined.

Reprint from: Molecular mechanism of 1,1-dichloroethylene toxicity: Excreted metabolites reveal different pathways of reactive intermediates. Archives of Toxicology, 42:159-169, 1979 by D. Reichert, H.W. Werner, M. Metzler, and D. Henschler with permission of Springer-Verlag New York, Inc.

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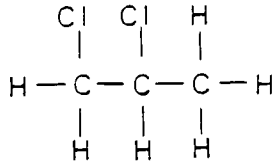
Reichert D, Werner HW, Metzler M, Henschler D. 1979. Molecular mechanism of 1,1-dichloroethylene toxicity: excreted metabolites reveal different pathways of reactive intermediates. Arch. Toxicol. 42(3):159-169.

1,2-DICHLOROPROPANE

$C_3H_6Cl_2$



CAS: 000078875

Syn: alpha,beta-dichloropropane; propylene chloride; propylene dichloride; alpha,beta-propylene dichloride

Mol wt: 112.99 g/mol

bp: 96.37°C (at 760 mm Hg)

vp: 50.8 mm Hg (at 25°C)

Jones and Gibson (1980) studied the metabolism of 1,2-dichloropropane in the rat and proposed a metabolic pathway (see Figure 1). Urinary metabolites of 1,2-dichloropropane (20 mg/kg administered orally for 4 days or in a single 100 mg/kg intraperitoneal injection) were identified by thin layer chromatography as N-acetyl-S-(2-hydroxypropyl)cysteine, the major metabolite (25%-35%), N-acetyl-S-(2,3-dihydroxypropyl)cysteine, and beta-chlorolactate. 1,2-Dichloropropane excreted unchanged by the lung was identified in the 0-3 hour expired air sample (5% of the dose) and in the 9-18 hour sample (5% of the dose) after a single 100 mg/kg intravenous injection.

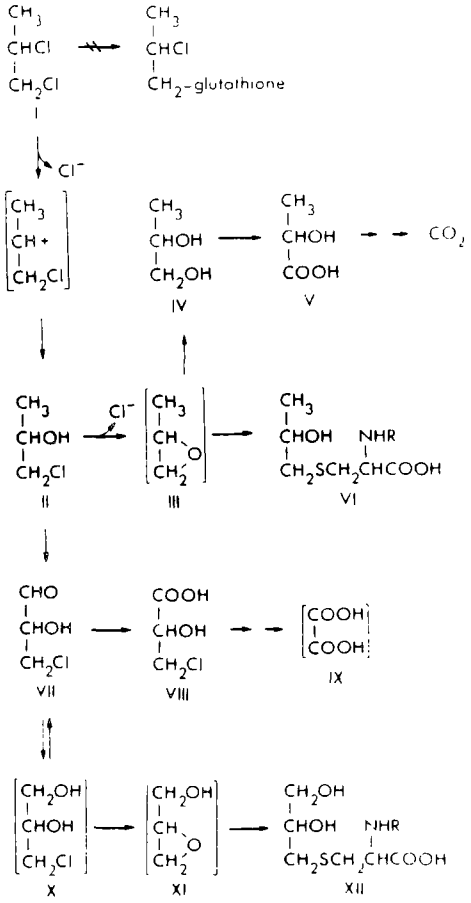


Fig. 1. The proposed metabolic pathways of 1,2-dichloropropane in the rat. (Compounds in parentheses are proposed intermediates).

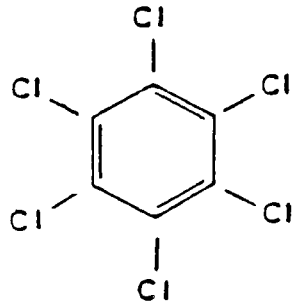
Reprinted from: 1,2-Dichloropropane: Metabolism and fate in the rat. Xenobiotica, 10(11):835-846, 1980 by A.R. Jones and J. Gibson with permission of Taylor and Francis, Ltd.

REFERENCE

Jones AR, Gibson J. 1980. 1,2-Dichloropropane: metabolism and fate in the rat. Xenobiotica 10(11):835-846.

HEXACHLOROBENZENE

C_6Cl_6



CAS: 000118741

Syn: HCB; perchlorobenzene

Mol wt: 284.79 g/mol

bp: 322-326°C (at 760 mm Hg)

vp: 9.84 mm Hg

Hexachlorobenzene is metabolized to pentachlorophenol (Koss & Koransky, 1978; Yang et al. 1978; Rozman et al. 1978) as well as tetrachlorohydroquinone and pentachlorothiophenol (Koss & Koransky, 1978), 2,4,5-trichlorophenol (Renner & Schuster, 1977), pentachlorobenzene, (Yang et al. 1978; Rozman et al. 1978), and tetrachlorobenzene (Rozman et al. 1978).

Lunde and Bjorseth (1977) measured the level of hexachlorobenzene in the blood of three occupational groups: Group A, 9 employees with no occupational exposure to chlorinated hydrocarbons; Group B, 9 workers in a plant producing vinyl chloride; Group C, 17 employees in a plant producing magnesium where chlorinated hydrocarbons are used in the process. The average value for hexachlorobenzene in the blood showed little difference between Group A (1.04 ppb) and B (1.54 ppb) but was significantly higher in Group C (29.61 ppb).

Koss et al. (1976) as cited in Koss and Koransky (1978) studied the metabolism of ^{14}C hexachlorobenzene in female rats following intraperitoneal injection (1.42 mmol/kg). Seven percent of the label was excreted in the urine and 27% in the feces. Almost all of the urinary radioactivity was contained in metabolites with 1% unchanged hexachlorobenzene while 69% of the fecal radioactivity was unchanged hexachlorobenzene. Hexachlorobenzene metabolites included pentachlorophenol, tetrachlorohydroquinone, and pentachlorothiophenol. Renner and Schuster (1977) identified 2,4,5-trichlorophenol as a urinary metabolite of hexachlorobenzene in rats after dietary administration.

Yang et al. (1978) studied the metabolism of hexachlorobenzene in rats and monkeys. Two male Sprague-Dawley rats were administered an intravenous dose of 1.3 uCi ^{14}C hexachlorobenzene (approximately 0.1 mg) and were sacrificed 2 days later. One percent of the administered dose was excreted in the feces and 0.2% was excreted in urine. Most of the radioactivity was retained in the animal with the highest concentration found in fat tissue. Three female rhesus monkeys were administered an intravenous dose of 24.7 (0.38 mg/kg), 26.2 (0.32 mg/kg), or 12.9 (0.22 mg/kg) uCi of ^{14}C hexachlorobenzene and

were sacrificed at 100 days, 6 months, and 1 year, respectively. Radioactivity was widely distributed with the fat and bone marrow containing the highest levels. Pentachlorophenol was identified as a major fecal metabolite. Traces of pentachlorobenzene were also identified.

Rhesus monkeys were also used by Rozman et al. (1978) to study chronic low dose exposure to hexachlorobenzene (11 mg/day) in the diet. Fecal excretion was 99% hexachlorobenzene, 1% pentachlorobenzene, and trace levels of pentachlorophenol. The main urinary metabolite was pentachlorophenol (50%-75%) with hexachlorobenzene, pentachlorobenzene, and tetrachlorobenzene also present. In one male monkey sacrificed after 18 months of feeding, the highest concentrations of hexachlorobenzene were present in the fat, bone marrow, thymus, and adrenal cortex.

Ofstad et al. (1978) studied the uptake and accumulation of hexachlorobenzene by different species of fish exposed to waters polluted by industrial chemicals. Homogenates of whole fish or fish fillets and liver were analyzed. The level of hexachlorobenzene in fish obtained near the pollutant source ranged from 5.2-208 ppm. In fish obtained at a greater distance, the range was 1.5-11 ppm. Hexachlorobenzene was found to accumulate to a greater degree in the liver than in the fillet tissue.

The remaining studies describe hexachlorobenzene effects as a contaminant to the study chemical.

Simon et al. (1979) studied the distribution and clearance of pentachloronitrobenzene in chickens. Chickens were administered 300 ppm pentachloronitrobenzene in the diet for 16 weeks. The concentrations of hexachlorobenzene were 19.8 ppm in fat, 7.47 ppm in liver, 7.95 ppm in egg yolk, 0.032 ppm in egg white, and 0.403 ppm in blood. The authors suggest that egg laying may be the primary route of hexachlorobenzene excretion.

Parker et al. (1980) analyzed the blood from 12 heifers exposed for 160 days to similar doses of pentachlorophenol made up of varying amounts of pure and contaminated compound. The levels of hexachlorobenzene in the blood increased as the relative amount in contaminated pentachlorophenol in the dose increased.

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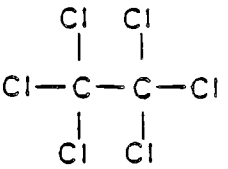
HEXACHLOROETHANE

C_2Cl_6



CAS: 000067721

Syn: carbon hexachloride; ethane hexachloride; 1,1,1,2,2,2-hexachloroethane; perchloroethane

Mol wt: 236.74 g/mol

bp: 186°C (at 777 mm Hg)

vp: 1.2 mm Hg (at 32.7°C)

Gorzinski et al. (1979) administered hexachloroethane orally to rats for 110 days at doses of 0, 1.5, 20, or 80 mg/kg. Males given 20 or 80 mg/kg/day showed histopathologic changes in the liver and kidneys and increased urinary excretion of uroporphyrin, creatinine, and delta-aminolevulinic acid. The latter two parameters were also increased in males at the 1.5 mg/kg level. Effects in females were limited to slight histopathologic changes in the liver at 80 mg/kg/day. Liver, kidney, blood, and adipose tissues from male rats after 57 days were analyzed. At all dose levels, the hexachloroethane concentration in male kidneys was significantly higher than females, consistent with the observed greater renal toxicity in males than females. The renal hexachloroethane concentrations were 1.4, 24.9, and 95.1 ug hexachloroethane/g in males, and 0.4, 0.7, and 2.0 ug hexachloroethane/g in females for the 1.5, 20, and 50 mg/kg doses, respectively. Hexachloroethane was cleared by apparent first-order kinetics with a half-life of 2 to 3 days.

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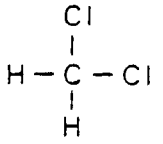
METHYLENE CHLORIDE

CH_2Cl_2



CAS: 000075092

Syn: methane dichloride; dichloromethane; methylene bichloride; methylene chloride; methylene dichloride

Mol wt: 84.93 g/mol

bp: 40°C (at 760 mm Hg)

vp: 430.4 mm Hg (at 25°C)

Methylene chloride is metabolized to carbon monoxide and carbon dioxide (Rodkey and Collison, 1977b; Anders et al. 1977; Kubic and Anders, 1978; Ahmed et al. 1980). An alternative metabolic pathway to formaldehyde and an inorganic halide is discussed by Ahmed et al. (1980).

Engstrom and Bjurstrom (1977) devised a method for determining methylene chloride concentration in human subcutaneous adipose tissue. Twelve males were exposed for 1 hour to 260 mg/m^3 methylene chloride while engaged in light exercise. Alveolar air samples were taken during and after exposure and venous blood samples were taken throughout the experiment. Adipose tissue samples were taken from the gluteal region immediately after exposure and 1, 2, 3, and 4 hours later. Subjects with a larger amount of body fat/kg body weight displayed a larger total methylene chloride uptake but a lower uptake/kg body weight.

Rodkey and Collison (1977a) measured carbon monoxide production after methylene chloride administration using a closed rebreathing system. Methylene chloride was injected into the system, vaporized, and inhaled by rats. Methylene chloride caused an immediate increase in carbon monoxide production with a simultaneous disappearance of methylene chloride from the air. Methylene chloride had a half-life of 25 minutes with only 2% remaining after 90 minutes. Methylene chloride injected intraperitoneally caused carbon monoxide formation identical to that caused by inhalation, however, no methylene chloride was present in the air. The role of intestinal bacteria on carbon monoxide production by methylene chloride was studied, but the presence or absence of bacteria had no effect on production levels.

Using the same system as described above, Rodkey and Collison (1977b) investigated whether increased carbon monoxide production after methylene chloride occurred due to direct metabolism of methylene chloride or to an increased rate of carbon monoxide formation from endogenous carbon sources. Sprague-Dawley rats were studied in a closed rebreathing system with exhaled

carbon monoxide and carbon dioxide collected separately. Labelled methylene chloride was administered at a single dose of 0.2 mmol/kg and the rats remained in the system for a least 7 hours. The average amount of administered label recovered as (^{14}C)-carbon monoxide was 47%, compared to 29% as (^{14}C) carbon dioxide. No radioactivity was recovered in any tissues tested. Extending the study to 15 hours did not increase the amount of carbon monoxide or carbon dioxide, suggesting that all of the methylene chloride was metabolized.

Withey and Collins (1980) studied the pharamcokinetics of methylene chloride in male Wistar rats. Blood samples were collected from rats administered 3, 6, 9, 12, or 15 mg/kg methylene chloride intravenously. Only at the 15 mg/kg dose did tissue samples produce meaningful kinetic data.

Anders et al. (1977) investigated the metabolism of methylene chloride in rats. A cytochrome P-450 dependent system seemed to be responsible for metabolizing methylene chloride to carbon monoxide. Methylene chloride was covalently bound to both microsomal lipid and protein with similar reaction kinetics to carbon monoxide formation. This suggests that formyl halide is a common intermediate acting either as an acylating agent or decomposing to carbon monoxide. Methylene chloride may also be converted to formaldehyde or formic acid and an inorganic halide in the hepatic cytosolic fraction with glutathione (GSH) as cofactor. This reaction is inhibited by reagents which react with sulfhydryl groups and known gluthathione transferase substrates. Halide displacement is the rate limiting step.

Kubic and Anders (1978) studied the metabolism of methylene chloride *in vitro* with rat liver microsomal fractions. Methylene chloride was converted to carbon dioxide and to carbon monoxide at a rate of 0.2 and 16.7 nmol/mg of protein/min, respectively. Carbon monoxide was the principal metabolite.

Ahmed et al. (1980) summarized the metabolism studies on methylene chloride. Methylene chloride is metabolized to carbon monoxide in animal systems both *in vivo* and *in vitro*. *In vitro* studies show that a cytochrome P-450 dependent enzyme system localized in the hepatic microsomal fraction is involved in the biotransformation of methylene chloride to carbon monoxide. An alternative metabolic pathway of methylene chloride to formaldehyde and an inorganic halide is localized in the hepatic cytosol fraction and requires glutathione for maximal activity.

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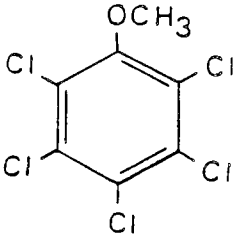
PENTACHLOROANISOLE

$C_7H_3Cl_5O$



CAS: 001825214

Syn: pentachloromethoxybenzene; 2,3,4,5,6-pentachloroanisole; methyl pentachlorophenate

Mol wt: 280.34 g/mol

Glickman et al. (1977) quantified the uptake, elimination, and metabolism of pentachloroanisole in rainbow trout. Comparison of uptake rates of pentachloroanisole and its known metabolite, pentachlorophenol, in blood, liver, muscle, and fat of fish exposed to 0.024 mg/liter (14-C)-pentachloroanisole (12 hours) or 0.026 mg/liter (14-C)-pentachlorophenol (24 hours) showed a much more rapid concentration of pentachloroanisole in fat and a greater liver concentration of pentachlorophenol. The high retention time of pentachloroanisole in fish probably reflected its high lipid solubility. Pentachloroanisole half-lives were 6.3, 6.9, 23.4, and 6.3 days in blood, liver, fat, and muscle, respectively, compared to pentachlorophenol half-lives of 6.2, 9.8, 23.7, and 6.9 hours, respectively. Pretreatment of fish with piperonyl butoxide decreased the conversion of pentachloroanisole by one third. Pentachloroanisole was rapidly taken up from water and assimilated in tissues. Pentachloroanisole could be demethylated in vivo, and piperonyl butoxide inhibited demethylation to pentachlorophenol.

Vodicnick et al. (1980) dosed mice with a single 20 mg/kg intraperitoneal injection of (^{14}C)-pentachloroanisole and recovered approximately 50% of the ^{14}C label in excreta (urine (88-93%) + feces). ^{14}C was eliminated with no unchanged pentachloroanisole detected in urine or feces, suggesting pentachloroanisole demethylation to pentachlorophenol prior to conjugation and/or excretion. Very little free pentachlorophenol was eliminated in urine while 30% of the fecal label was in the nonconjugated form. Radioactive label was rapidly concentrated in liver and adipose tissue. Liver displayed the longest tissue half-life (19 hours) and biphasic elimination. Other tissues showed rapid elimination, with half-lives ranging from 5 to 10 hours.

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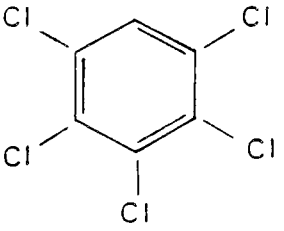
PENTACHLOROBENZENE

C_6HCl_5



CAS: 000608935

Syn: quintachlorobenzene; 1,2,3,4,5-pentachlorobenzene

Mol wt: 250.34 g/mol

bp: 277°C (at 760 mm Hg)

vp: 1.04 mm Hg (at 98.6°C)

Pentachlorobenzene is metabolized primarily to tetrachlorophenol (Leber et al. 1977; Koss and Koransky, 1978) in addition to pentachlorophenol, a hydroxylated chlorothio compound, and tetrachlorohydroquinone (Koss and Koransky, 1978).

Lunde and Bjorseth (1977) measured the level of pentachlorobenzene in the blood of three occupational groups: Group A, 9 employees with no occupational exposure to chlorinated hydrocarbons; Group B, 9 workers in a plant producing vinyl chloride; Group C, 17 employees in a plant producing magnesium where chlorinated hydrocarbons are used in the process. The average value for pentachlorobenzene in the blood showed no difference between Group A (0.00 ppb) and B (0.00 ppb) and was only slightly higher in Group C (0.15 ppb).

Koss and Koransky (1978) studied pentachlorobenzene metabolism in female rats. Urine and fecal samples were taken for 4 days after a single intraperitoneal injection of 403 umol pentachlorobenzene/kg. Only 3% of the injected pentachlorobenzene was excreted unchanged. The major metabolites excreted in the urine and feces were 2,3,4,5-tetrachlorophenol, a hydroxylated chlorothio compound, and pentachlorophenol. Tetrachlorohydroquinone was found in the urine. These metabolites were also present in tissue samples.

Leber et al. (1977) investigated the pharmacokinetic properties and metabolic fate of pentachlorobenzene in 5 male rhesus monkeys. A single oral dose of 20 mg/monkey of labelled pentachlorobenzene was administered and the concentration of the radioactivity was determined in the blood, urine, and feces. Tetrachlorophenol was determined as the main urinary metabolite. Most of the labelled pentachlorobenzene was excreted unchanged in the feces.

The uptake and accumulation of pentachlorobenzene in different species of fish obtained from polluted water was studied by Ofstad and colleagues (1978). Whole fish or fish fillets and liver samples were analyzed. The level of pentachlorobenzene ranged from 0.2-24.0 ppm in fish obtained near the polluting source. In fish obtained at a greater distance, the concentration

ranged from 0.1 to 1.9 ppm. Pentachlorobenzene accumulated to a greater degree in the liver than in the fillet tissue.

The remaining studies involve pentachloronitrobenzene metabolism to pentachlorobenzene, or pentachlorobenzene-contaminated pentachloronitrobenzene exposure to test animals.

The biotransformation of pentachloronitrobenzene was studied in rhesus monkeys by Koegel et al. (1979a). Metabolites were analyzed in urine and feces after single oral doses of 2 or 91 mg/kg or after chronic feeding of 2 ppm in the diet for 71 days. Due to its extensive metabolism, pentachloronitrobenzene did not accumulate in the tissue but was rapidly eliminated. Pentachlorobenzene was one of the major metabolites produced. After a single oral dose of 2 mg/kg pentachloronitrobenzene, pentachlorobenzene comprised 11.7% of the urinary extract and 1.0% of the fecal extract. Similar percentages of pentachlorobenzene were found in urine and feces after a single oral dose of 91 mg/kg pentachloronitrobenzene and after chronic feeding (Koegel et al., 1979b).

Simon et al. (1979) investigated the distribution and clearance of pentachloronitrobenzene with its contaminants in chickens. For 16 weeks, 110 Comet Red hens received pentachloronitrobenzene mixed with their food in doses of 0, 0.5, 1, 5, 15, 75, or 300 ppm. Seventy-five White Leghorn hens were exposed in the same manner to doses of 0, 15, 75, or 300 ppm. The concentrations of pentachlorobenzene deposited in the tissues of the 300 ppm exposed Comet Red hens after 16 weeks were 1.32 ppm in fat, 0.276 ppm in liver, 0.013 ppm in blood, 0.355 ppm in egg yolk, and 0.015 ppm in excreta; tissue levels of pentachlorobenzene were similar in the White leghorn. Residues of pentachlorobenzene were detectable in the egg yolk for 1 year after exposure ceased. Egg laying is proposed as the main route of pentachlorobenzene excretion.

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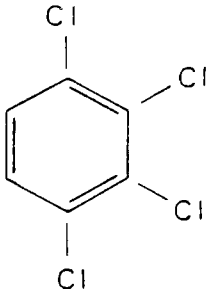
TETRACHLOROBENZENE

$C_6H_2Cl_4$

Mol wt: 215.88 g/mol

1,2,3,4-tetrachlorobenzene



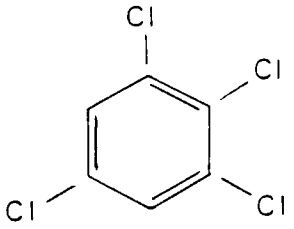
CAS: 000634662

Syn: benzene, 1,2,3,4-tetrachloro-

bp: 254°C (at 760 mm Hg)

vp: 1.04 mm Hg (at 68.5°C)

1,2,3,5-tetrachlorobenzene



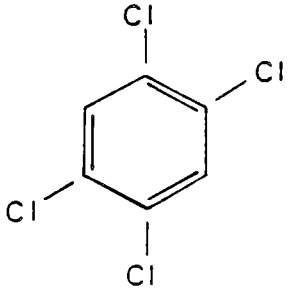
CAS: 000634902

Syn: benzene, 1,2,3,5-tetrachloro-

bp: 246°C (at 760 mm Hg)

vp: 1.06 mm Hg (at 58.2°C)

1,2,4,5-tetrachlorobenzene



CAS: 000095943

Syn: benzene, 1,2,4,5-tetrachloro-

bp: 243-246°C (at 760 mm Hg)

vp: 0.1 mm Hg (at 25°C)

1,2,4,5-Tetrachlorobenzene steady state parameters and elimination rate constants in fat and plasma were determined by Braun et al. (1978) in a 2-year study of daily oral administration of 5 mg/kg tetrachlorobenzene to beagle dogs followed by a 20 month recovery phase. The tetrachlorobenzene uptake rate constants were very high during the study and the clearance rates were similar: 6.64×10^{-3}/day ($\pm$ 8.2×10^{-4}) for plasma and 6.01×10^{-3}/day ($\pm 5.8 \times 10^{-4}$) for fat. The corresponding half-life values were 104 and 111 days. Tetrachlorobenzene had an extremely high affinity for fat, with the fat to plasma ratio (F/P) of 650 after 1 month decreasing to 280 after 24 months (98% saturation level). Plasma tetrachlorobenzene levels increased as fat attained saturation thus increasing tetrachlorobenzene concentrations in low affinity compartments such as the liver and delaying the onset of apparant toxicity. The F/P ratio steadily increased in the post-exposure period (20 months, F/P = 2000) as tetrachlorobenzene was cleared faster from plasma and

other lower affinity compartments, possibly accounting for the reversibility of toxicity.

Ofstad et al. (1978) investigated the bioaccumulation of polychlorinated benzenes (including tetrachlorobenzene) in various fish species consumed by humans. Uptake and accumulation were very efficient, and species differences were observed. Comparison of liver and fillet oil extracts showed that chlorinated benzene accumulated to a greater extent in the liver (0.8 ppm in cod) due to a slower exchange of pollutants from the liver than from the muscle tissue. The mean tetrachlorobenzene concentrations in fat ranged from 0.1-1.4 ppm in cod, whiting, plaice, eel, and sprat from the contaminated Frierfjord area, and were less than or equal to 0.1 ppm in the Eidangerfjord.

REFERENCES

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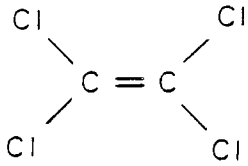
Ofstad EB, Lunde G, Martinsen K, Rygg B. 1978. Chlorinated aromatic hydrocarbons in fish from an area polluted by industrial effluents. Sci. Total Environ. 10(3):219-230.

TETRACHLOROETHYLENE

C_2Cl_4



CAS: 000127184

Syn: carbon bichloride; carbon dichloride; ethylene tetrachloride; perchloroethylene; tetrachloroethylene; tetrachloroethene; 1,1,2,2-tetrachloroethylene

Mol wt: 165.83 g/mol

bp: 121°C (at 760 mm Hg)

vp: 18.0 mm Hg (at 25°C)

Tetrachloroethylene is metabolized via the P-450 enzyme system (Costa and Ivanetich, 1980) yielding trichloroacetic acid as the major metabolite (Costa & Ivanetich, 1980; Ikeda, 1977; Monster, 1979). One study (Pegg et al. 1979) reports that oxalic acid is the major metabolite of tetrachloroethylene.

Monster (1979) exposed human volunteers for 4 hours to tetrachloroethylene at varied concentrations in air: 70 ppm at rest; 140 ppm at rest; and 140 ppm at rest and during work. The lung clearance rate decreased over the course of the experiment, primarily due to the insignificant metabolism (2%) of tetrachloroethylene to trichloroacetic acid. Adipose tissue absorbed a greater portion of tetrachloroethylene than any other tissue. Metabolism of tetrachloroethylene proceeded by oxidation to perchloroethylene oxide, rearrangement to trichloroacetyl chloride, and hydrolysis to trichloroacetic acid. Trichloroacetic acid reached a peak concentration approximately 20 hours after exposure. Only 2% of the administered tetrachloroethylene was metabolized, primarily by the liver, while 95% was excreted unchanged by the lung.

In a study of tetrachloroethylene metabolism in humans, Ikeda (1977) also determined trichloroacetic acid to be the main urinary metabolite. Thirty-four male workers who were exposed to tetrachloroethylene vapors while working in small, closed workrooms were studied. The biological half-life of the urinary metabolite was approximately 144 hours.

Gobbato and Mangiavacchi (1979) presented a mathematical model for simulating the respiratory absorption, tissue distribution, hepatic metabolism, and pulmonary and renal excretion of various industrial solvents. The validity of this model was substantiated by agreement between the theoretical results for tetrachloroethylene and experimental results described in the literature.

Pegg et al. (1979) studied the response in rats exposed to labelled tetrachloroethylene via oral dosing (1 or 500 mg/kg) or by inhalation (10 or 600 ppm for 6 hours). Seventy-two hours after administration, urine, blood, feces, expired air, and tissues were analyzed for radioactivity. Urine samples were also analyzed by HPLC for identification of metabolites. At the low doses, approximately 70% of the administered radioactivity was recovered in the expired air as tetrachloro(^{14}C)ethylene, 26% was recovered as (^{14}C)-carbon dioxide, and nonvolatile metabolites were recovered in the urine and feces. Approximately 3%-4% remained in the tissue. At the high dose, 89% of the radioactive label was eliminated in the expired air as tetrachloro(14C)ethylene, 9% was recovered as (^{14}C)-carbon dioxide and as metabolites in the urine and feces. Only 1%-2% was retained in the tissues. At both doses, the major urinary metabolite was identified as oxalic acid. Most of the radioactivity retained by the tissues was found in the liver, kidney, and fat.

Costa and Ivanetich (1980) investigated the binding to and metabolism of tetrachloroethylene by rat liver microsomal cytochrome proteins. The rate of tetrachloroethylene metabolism by microsomes was assayed by measuring the oxidation of NADPH. Identification of metabolic products showed trichloroacetic acid to be the major metabolite. Based on selective microsomal induction and inhibition, the P-450 enzyme system appears to be the primary enzyme system binding and metabolizing tetrachloroethylene.

Miyake (1978) fed muscle homogenates of tetrachloroethylene-exposed eels to rats. Concentrations of tetrachloroethylene in rat tissues were measured by gas chromatography. The highest levels were found in adipose tissue with a peak concentration at 6 hours. Tetrachloroethylene caused a decoupling action of the oxidative phosphorylation process in liver mitochondria.

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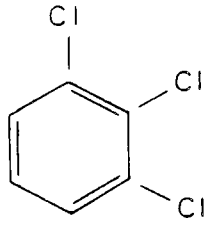
TRICHLOROBENZENE

$C_6H_3Cl_3$

Mol. wt: 181.45 g/mol

1,2,3-trichlorobenzene



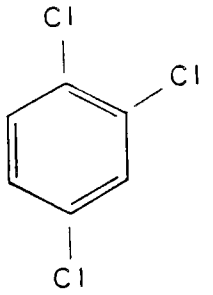
CAS: 000087616

Syn: vic-trichlorobenzene; 1,2,6-trichlorobenzene

bp: 218-219°C (at 760 mm Hg)

vp: 0.99 mm Hg (at 40°C)

1,2,4-trichlorobenzene



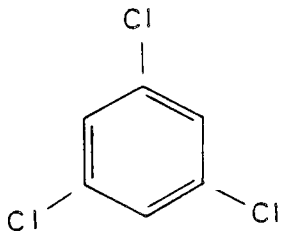
CAS: 000120821

Syn: unsym-trichlorobenzene

bp: 213.5°C (at 760 mm Hg); 84.8°C (at 10 mm Hg)

vp: 1.04 mm Hg (at 38.4°C)

1,3,5-trichlorobenzene



CAS: 00108703

bp: 108°C (at 763 mm Hg)

vp: 5.1 mm Hg (at 63.8°C)

1,2,4-Trichlorobenzene metabolism and body burden were studied in phenobarbital treated and starved rats by Smith et al. (1980) using ^{14}C labelled trichlorobenzene (1 mmol/kg/day) orally administered for 7 days. The highest trichlorobenzene concentration was found in fat tissue. ^{14}C appeared in urine through day 15 post-exposure (accounting for 72% total radioactivity) and in feces for 8 days after dosing (4%). Hepatic microsomal enzymes, primarily those responsible for p-nitroanisole demethylation and EPN detoxification, were elevated for at least 16 days post-exposure. NADPH-cytochrome c reductase activity and cytochrome P-450 content declined rapidly after cessation of dosing. Phenobarbital treatment or starvation immediately after trichlorobenzene exposure hastened its mobilization, metabolism, and excretion.

Melancon et al. (1980) exposed rainbow trout and carp to radiolabelled trichlorobenzene (0.018 mg/liter) for 8 hours or 35 days and traced the ^{14}C bioaccumulation in tissues. After 8 hours, liver, muscle, and blood

concentrations of ^{14}C were 102, 51, and 33 times greater, respectively, than concentrations in the exposure water; corresponding half-lives were 0.4, 0.4, and 0.02 days. Similar results were found for chronically exposed fish. Bile levels were 104-240 times greater than the initial water levels. During the 35-day exposure, maximum ^{14}C levels were 389, 89, and 84 times greater than the initial water concentration for liver, muscle, and blood with longer elimination half-lives of 56, 47, and less than 1 day, respectively. Bile concentrations were 500-1400 times higher than water concentrations during the exposure period and approximately 100 times higher afterwards. Table 1 shows tissue levels of ^{14}C and biotransformation products in trout and carp after 24 hours of exposure to trichlorobenzene. Bile and liver had the greatest amount of radioactivity, with the bile containing a high proportion of polar compounds suggestive of biotransformed conjugates. Blood had the only other significant concentration of polar metabolites. The hepatic mixed-function oxidase system inducer, beta-naphthoflavone injected intraperitoneally (100 mg/kg) increased the levels of ^{14}C in the bile; over 90% of the radioactivity was highly polar transformation products.

Table 1. Tissue levels of (^{14}C) TCB and biotransformation products in rainbow trout and carp after exposure to aqueous (^{14}C) TCB for 24 hr.

	Trout[a]	Trout[b]			Carp[c]		
	[^{14}C]TCB and metabolites	[^{14}C]TCB and metabolites	Percent in water phase[d]		[^{14}C]TCB and metabolites	Percent in water phase[d]	
Tissue	(μg/g or μg/ml)	(μg/g or μg/ml)	pH 7.4	pH 11	(μg/g or μg/ml)	pH 7.4	pH 11
Bile	38.2 ± 3.4	6.8 ± 0.7	45	52	18.1 ± 3.0	61	58
Blood	5.8 ± 1.2	1.3 ± 0.1	8.9 ± 2.3	24.8 ± 4.6	2.8 ± 0.2	11.2 ± 2.2	18.5 ± 3.1
Plasma		1.4 ± 0.1			3.0 ± 0.2		
Muscle	9.6 ± 2.1	2.5 ± 0.3	2.1		2.2 ± 0.1		
Liver	19.3 ± 1.2	4.0 ± 0.4	2.2	2.6	11.3 ± 2.4	3.4	2.6
Kidney		1.8 ± 0.7	3.0	1.6	7.6 ± 1.2		

[a] A group of 61-g (average weight) trout was exposed to [^{14}C]TCB at 0.40 mg/l.
[b] A group of 139-g (average weight) trout was exposed to [^{14}C]TCB at 0.24 mg/l.
[c] A group of 349-g (average weight) trout was exposed to [^{14}C]TCB at 0.20 mg/l.
[d] After shaking with hexane.

Reprinted from: Uptake, metabolism, and elimination of ^{14}C-labeled 1,2,4-Trichlorobenzene in rainbow trout and carp, Journal of Toxicology and Environmental Health, 6:645-658, 1980 by M.J. Melancon and J.J. Lech with permission of Hemisphere Publishing Co.

Ofstad et al. (1978) found trichlorobenzene accumulations ranging from 0.1-4.0 ppm in fish from the Frierfjord area. Analysis of oil extracted from liver and fillet indicated that the chlorinated compounds accumulate to a larger extent in the liver than in muscle.

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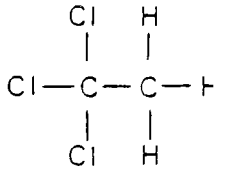
Melancon MJ, Lech JJ. 1980. Uptake, metabolism, and elimination of ^{14}C-labelled 1,2,4-trichlorobenzene in rainbow trout and carp. J. Toxicol. Environ. Health 6:645-658.

Ofstad EB, Lunde G, Martinsen K, Rygg B. 1978. Chlorinated aromatic hydrocarbons in fish from an area polluted by industrial effluents. Sci. Total Environ. 10(3):219-230.

Smith EN, Carlson GP. 1980. Various pharmacokinetic parameters in relation to enzyme-inducing abilities of 1,2,4-trichlorobenzene and 1,2,4-tribromobenzene. J. Toxicol. Environ. Health 6(4):737-749.

1,1,1-TRICHLOROETHANE

$C_2H_3Cl_3$



CAS: 000071556

Syn: methylchloroform; MC; alpha-trichloroethane

Mol wt: 133.41 g/mol

bp: 74.1°C (at 760 mm Hg)

vp: 121.3 mm Hg (at 25°C)

Monster (1979) exposed human volunteers for 4 hours to 1,1,1-trichloroethane gas at varying concentrations (70 ppm at rest; 140 ppm at rest; 140 ppm at work and rest). Trichloroethane uptake was largely determined by its solubility in blood and by its metabolism. Trichloroethane solubility in blood was expressed as the ratio of the concentration in blood (mg/liter) to the concentration in alveolar air (mg/liter) or the blood/gas partition coefficient (b/g) (measured value = 5). The lung clearance rate (uptake/minute) for trichloroethane decreased significantly over the course of exposure. The low partition coefficient and low metabolism (3.5%) promoted a rapidly attained counter pressure to trichloroethane absorption. Venous blood concentrations were lower than arterial blood concentrations during exposure due to trichloroethane entry into tissues, and were slightly higher than arterial blood concentrations after exposure (2 and 20 hours) as tissues released the compound. Adipose tissue had a long half-life for saturation (25 hours) presumably due to a small perfusion coefficient (0.4 liters/min) and had a high capacity for trichloroethane absorption (volume x solubility = 800 liters). Net absorption was low compared to other tissues (4 hours exposure). After exposure, the redistribution of trichloroethane to adipose tissue was minor due to the rapid release of solvent from tissues and blood to air. Biotransformation of trichloroethane to trichloroethanol (TCE) was low; only 3.5% of all metabolites were detected in urine and 80% of a 70 ppm exposure was eliminated in expired air. Therefore the overall capacity for trichloroethane absorbance was small over a 4-hour exposure. The metabolism of the chemical as proposed by the author is illustrated in Figure 1.

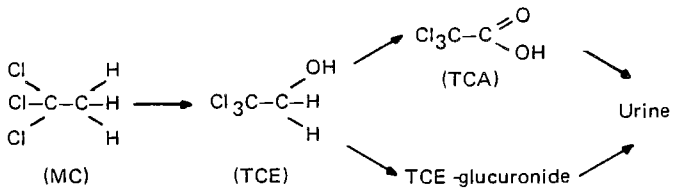


Fig. 1. Biotransformation of 1,1,1-trichloroethene (MC).

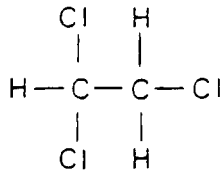
Reprinted from: Difference in uptake, elimination, and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane, and tetrachloroethylene. International Archives of Occupational and Environmental Health, 42:311-317, 1979 by A.C. Monster with permission of Springer-Verlag, Heidelberg.

REFERENCE

Monster AC. 1979. Uptake, metabolism and excretion of trichloroethylene, 1,1,1,-trichloroethane and tetrachloroethylene. Int. Arch. Occup. Environ. Health, 42(3-4):311-318.

1,1,2-TRICHLOROETHANE

$C_2H_3Cl_3$



CAS: 000079005

Syn: ethane trichloride; beta-trichloroethane; 1,1,2-trichloroethane; vinyl trichloride

Mol wt: 133.41 g/mol

bp: 113.77°C (at 760 mm Hg)

vp: 23.16 mm Hg (at 25°C)

The blood concentration of 1,1,2-trichloroethane was studied by Jakobson et al. (1977) in guinea pigs after intracutaneous, subcutaneous, or intraperitoneal injection. All three injection routes gave essentially the same blood concentration curves (see Figure 1). Percutaneous absorption concentrations were also measured. Equations with three exponential terms, with or without constants, were derived to describe the findings. No calculations were performed with data from subcutaneous or intracutaneous injection but the form of these two curves indicated similar, or possibly simpler, toxicokinetics compared to that for intraperitoneal injection. Blood concentration of 1,1,2-trichloroethane caused by percutaneous absorption gave a different curve, possibly due to a local effect on the skin rather than to a systemic effect.

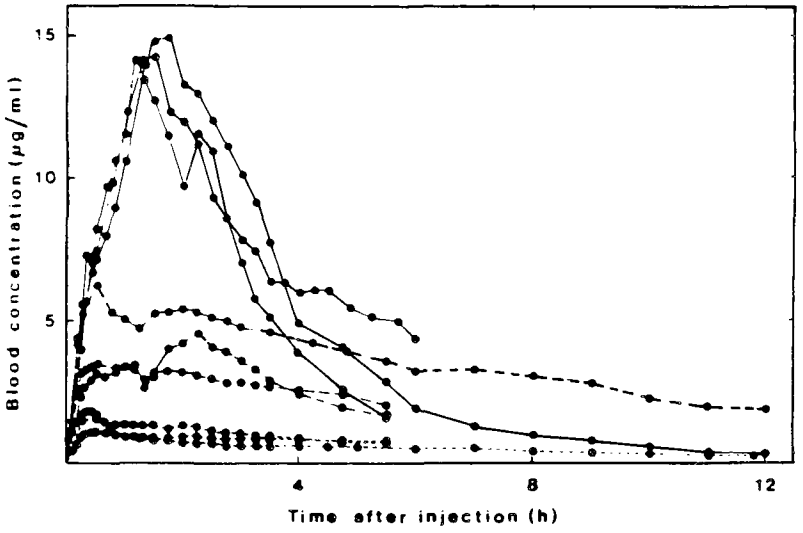


Fig. 1. Blood concentration after administration of 50 ul 1,1,2-trichloroethane in 9 guinea pigs (intraperitoneally●-●, subcutaneously●—●, intracutaneously●---●).

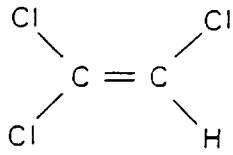
Reprinted from: Variations in the blood concentration of 1,1,2-trichloroethane by percutaneous adsorption and other routes of administration in the guinea pig. Acta Pharmacologica et Toxicologica, 41:497-506, 1977 by I. Jakobson, Bo Holmberg, and Jane E. Wahlberg with permission of the Scandinavian Pharmacological Societies.

REFERENCE

Jakobson I, Homberg B, Wahlberg, JE. 1977. Variations in the blood concentration of 1,1,2-trichloroethane by percutaneous absorption and other routes of administration in the guinea pig. Acta Pharmacol. Toxicol., 41(5):497-506.

TRICHLOROETHYLENE

C_2HCl_3



CAS: 000079016

Syn: acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethinyl trichloride; ethylene trichloride; TCE; TRI; trichloroethene; 1,1,2-trichloroethylene; 1,2,2-trichloroethylene; trilene

Mol wt: 131.39 g/mol

bp: 87°C (at 760 mm Hg)

vp: 72.9 mm Hg (at 25°C)

Trichloroethylene exposure occurs primarily through the lung where it is absorbed into the blood at a relatively high and constant rate. Trichloroethylene is metabolized primarily in the liver to trichloroethylene epoxide and then transformed to chloral hydrate which can be reduced to trichloroethanol or oxidized to trichloroacetic acid (Monster, 1977; Nomiyama & Nomiyama, 1979; Ikeda, et al. 1980). Trichloroethanol is transformed to a glucuronide, the main urinary metabolite, and is 2-7 times more abundant than urinary trichloroacetic acid (Artigue et al. 1978). Most trichloroethylene is excreted in the urine with only a small amount excreted by the lungs; a small amount is stored in adipose tissue (Monster, 1977).

In a study on human subjects, Monster (1979) exposed the subjects for 4 hours to trichloroethylene gas concentrations of 70 ppm at rest, 140 ppm at rest, and 140 ppm at rest and during work. A nearly constant high rate of absorption/minute of trichloroethylene resulted from the high partition coefficient (lambda b/g = 15) and rapid metabolism (75%). Trichloroethylene was metabolized to trichloroethanol and trichloroacetic acid. Trichloroethylene biotransformation occurred mainly in the liver. Maximum blood concentrations of trichloroacetic acid occurred 20-40 hours after exposure to trichloroethylene. Only 10% of a 70 ppm trichloroethylene exposure dose was eliminated in exhaled air; 21% appeared in the urine as trichloroacetic acid and 43% as trichloroethanol. Most of the trichloroethylene was excreted in the urine.

Smith (1978) found maximum urinary excretion of trichloroethylene metabolites 24-48 hours after determining levels of industrial exposure to trichloroethylene. He also found that retention increased with prolonged exposure. There were interindividual variations in the trichloroethylene metabolic rate, but the author suggested that urinary trichloroacetic acid was a good measure of trichloroethylene exposure.

In a study of 15 men who were divided into 3 groups based on exposures to different concentrations of trichloroethylene, Vesterberg et al. (1976) analyzed blood and urine samples for trichloroacetic acid and trichloroethanol. Trichloroacetic acid was noted after 30 minutes of exposure and increased linearly until 30 minutes after exposure ceased. Trichloroacetic acid and trichloroethanol were excreted in the urine and the amount correlated with the amount of exposure.

Fernandez et al. (1977) simulated the pulmonary absorption, distribution, and elimination of trichloroethylene in man, as well as the kinetics of formation and excretion of its metabolites, using a mathematical model. The results predicted by the model fit the author's data for exposed human subjects. In a follow-up study, Droz and Fernandez (1978) proposed another method of determining the body burden of trichloroethylene and rate of urinary excretion of metabolites. The body burden of trichloroethylene could be estimated by comparing the pre- and post-exposure urine or alveolar air samples to determine the rate of absorption.

Sato and Nakajima (1977) measured the rate constants for trichloroethylene absorption, metabolism, and excretion based on analysis of urinary metabolites. Four male volunteers were exposed to an atmosphere containing 100 ppm trichloroethylene for 4 hours. Blood and urine samples were taken at specific time intervals. The pharmacodynamics of trichloroethylene were described by a three compartment model.

Gobbato and Mangiavacchi (1979) presented a mathematical model for the simulation of the respiratory absorption, tissue distribution, hepatic metabolism and pulmonary and renal excretion of industrial solvents. A multicompartmental model formulated by the authors in a previous work was modified by considering hepatic metabolism and distribution of hydrosoluble metabolites in body fluids and renal excretion. The validity of the model was substantiated by agreement between theoretical results for trichloroethylene and experimental results available in the literature.

Nomiyama and Nomiyama (1979) studied the metabolism of intraperitoneally administered trichloroethylene in rats and rabbits. The primary metabolic pathway of trichloroethylene in the rat proceeded through chloral hydrate to trichloroethanol (35.6%). This conversion was essentially complete by the second day following a 10 mg/kg dose. Trichloroethanol also was the main metabolite (34.4%) in the rabbit, with only a trace amount of trichloroacetic acid excreted in the urine.

Ikeda et al. (1980) determined that NADPH and NAD were necessary to convert trichloroethylene to trichloroacetic acid in rat liver homogenates. The conversion was enhanced by both phenobarbital and 3-methylcholanthrene pretreatment. Trichloroethylene was oxidized to chloral hydrate, which occurred only in the microsomes. Chloral hydrate reduction to trichloroethanol occurred via NADPH-dependent enzymes found in the liver cytosol and was the primary metabolite. When 0.1 ml of trichloroethylene was incubated under complete incubation mixture conditions with 9,000 g supernatant for 60 minutes at 37°C, the following metabolites were measured: chloral hydrate (0.5 nmol/mg); trichloroethanol (6.9 nmol/mg); and trichloroacetic acid (0.3 nmol/mg). The cytosolic fraction catalyzed the oxidation of chloral hydrate

to trichloroacetic acid and the mitochondrial fraction had the highest specific activity but the microsomal fraction contributed only slightly to the formation of trichloroacetic acid.

Uehleke et al. (1977) incubated trichloroethylene and its suspected metabolites with suspensions of rat liver microsomes. Spectrophotometrically, only the spectrum of trichloroethylene epoxide matched that of metabolized trichloroethylene. The maximal absorption was observed with 1 mM NADPH and 1 mM trichloroethylene.

Withey and Collins (1980) studied the pharmacokinetics of trichloroethylene metabolism in male Wister rats. Varied doses (3, 6, 9, 12, or 15 mg/kg) of trichloroethylene were administered intravenously and blood samples were collected at selected time intervals. Meaningful kinetic data were found at only the highest dose level (15 mg/kg), indicating elimination by a three compartment model.

Pfaffenberger et al. (1979), using gas-liquid chromatography studied the distribution of trichloroethylene between rat blood serum and adipose tissue. Trichloroethanol was rapidly eliminated in the urine. Trichloroacetic acid was not as readily eliminated and was decomposed to carbon dioxide and chloroform as shown in Figure 1. Doses of 1 or 10 mg/kg trichloroethylene led to serum levels of chloroform of 1600 or 9300 mg/l, respectively. Fat levels were approximately 5% of these values. Trichloroethylene blood levels were essentially zero, implying a rapid metabolism or lipid storage. Fat levels were 0.3 or 20 mg/g. Chloroform levels dropped rapidly to below 2% of the peak levels several days after cessation of dosing.

Traylor et al. (1977) incubated trichloroethylene with liver microsomes from phenobarbital or 3,4-benzo(a)pyrene pretreated rats, with NADPH and oxygen. Production of carbon monoxide (CO) was determined by ultraviolet and infrared spectroscopy and demonstrated by the formation of carboxyhemoglobin. Increasing the trichloroethylene incubate concentration or increasing the incubation time increased CO levels as measured by the reduced P-450/CO differential spectrum. A proposed chemical pathway for conversion of cytochrome trichloroethylene to carbon monoxide in the presence of O_2 and NADPH is shown in Figure 2.

Dalby and Bingham (1978) ventilated rat lungs with 30 to 45 ppm trichloroethylene and determined a blood/air partition coefficient of approximately 26. Blood samples showed the presence of trichloroethanol 15-30 minutes after exposure and a linear increase with exposure duration. Pretreatment of rats with phenobarbital for 4 days enhanced trichloroethanol formation by approximately 2-fold.

Allemand et al. (1978) studied the *in vivo* and *in vitro* binding of trichloroethylene metabolites to rat liver proteins. Phenobarbital increased binding while cobaltous chloride, piperonyl butoxide pretreatments, or CO *in vitro* decreased binding. Hepatic glutathione levels intially decreased by 65% but later increased to 108% of the initial level after *in vivo* administration of 2 mg/kg trichloroethylene. Trichloroethylene expoxide was proposed as the reactive metabolite responsible for macromolecular binding, glutathione depletion, centrilobular necroses, and hepatotoxicity.

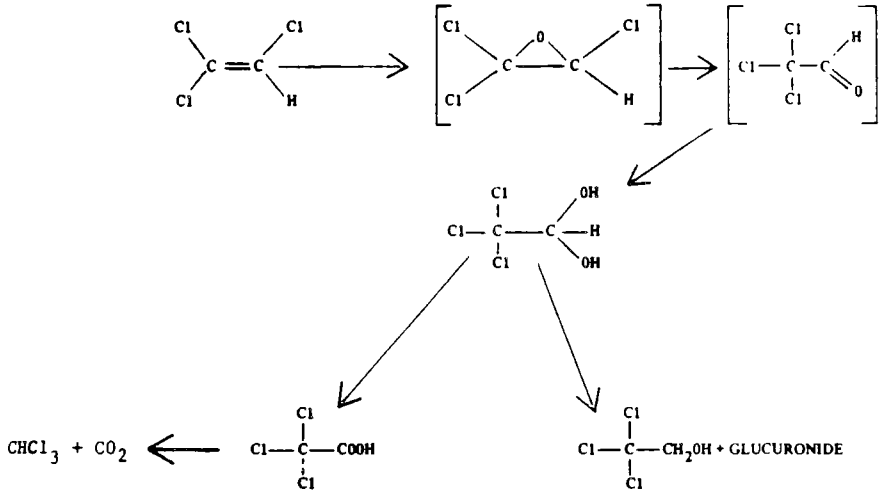


Fig. 1. Metabolic route by which trichloroethylene is converted into trichloroethanol and trichloroacetic acid. As indicated, trichloroacetic acid decomposes into carbon dioxide and chloroform under the analysis conditions given in the text.

Reprinted from: Distribution study of volatile halogenated organic compounds between rat blood serum and adipose tissue using a purge/trap procedure. International Journal of Environmental Analytical Chemistry, 8(1):55-66, 1980 by C.D. Pfaffenberger, A.J. Peoples, and H.F. Enos with permission of Gordon and Breach Science Publishers

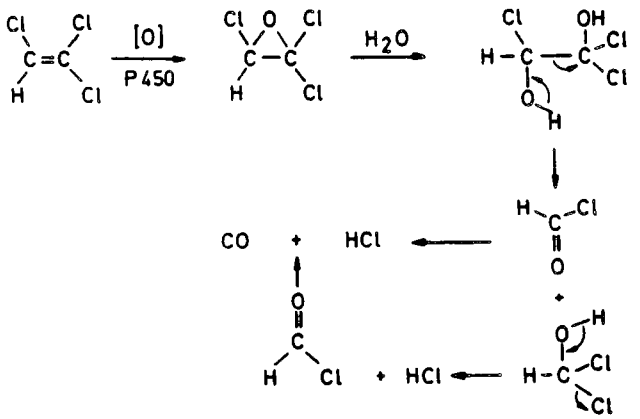


Fig. 2. Possible chemical pathway for conversion of trichloroethylene to carbon monoxide in the presence of NADPH.

Reprinted from: Conversion of trichloroethylene to carbon monoxide by microsomal cytochrome P-450, International Symposium Microsomes and Drug Oxidations, Proceedings, 615-621, 1976 by P.S. Traylor, W. Nastainczyk, and V. Ulrich with permission of Pergammon Press, Inc.

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APPENDIX

Summary Table of Experimental Data

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
3 umol bromobenzene incubated in a NADPH-generating system with in vitro liver microsomes (1.0-1.4 mg protein)	Rats					Liver microsomal fraction	* specific activities of enzymes (nmol/min/100 mg protein)	Lau SS et al. 1979
I.P. pretreatment								
control		o-bromophenol				7.1*		
		p-bromophenol				74.3*		
50 mg/kg phenobarbitol		o-bromophenol				64.4*		
		p-bromophenol				455.6*		
20 mg/kg 3-methylcholanthrene		o-bromophenol				251.4*		
		p-bromophenol				60.1*		
60 mg/kg beta-naphthoflavone		o-bromophenol				169.7*		
		p-bromophenol				52.0*		
3 umol bromobenzene incubated with liver microsomes (1.0-1.4 mg protein)	Mice							
I.P. pretreatment								
control		o-bromophenol				35.8*		
		p-bromophenol				35.8*		
20 mg/kg 3-methylcholanthrene		o-bromophenol				105.5*		
		p-bromophenol				47.8*		
40 mg/kg beta-naphthoflavone		o-bromophenol				133.5*		
		p-bromophenol				47.5*		
3 umol bromobenzene incubated with liver microsomes (1.0-1.4 mg protein)	Mice**						** cytochrome P-448 noninducible strain	
I.P. pretreatment								
control		o-bromophenol				60.0*		
		p-bromophenol				45.6*		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
50 mg/kg phenobarbital		o-bromophenol p-bromophenol				260.0* 753.0*		
20 mg/kg 3-methylcholanthrene		o-bromophenol p-bromophenol				51.5* 61.7*		Lau SS et al. 1979 (cont.)
40 mg/kg beta-naphthoflavone		o-bromophenol p-bromophenol				42.0* 66.2*		
25 ul tritium labelled bromobenzene in solution incubated with liver microsomes	Rats	bromobenzene				Liver microsomes 0.864*	* rate of disappearance (nmol/mg protein/min)	Wiley RA et al. 1979
1 mM final concentration tritium labelled bromobenzene incubated with liver microsomes								
Pretreatment								
control i.p. phenobarbital		bromobenzene				3.99** 37.78**	** radioactive covalent binding (pmol/mg protein/min)	

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
60 umol bromoform incubated in NADPH-generating system with liver fractions:	Rats					Liver fractions		Ahmed AE et al. 1977
cytosol (contain 5-7 mg protein)		carbon monoxide				0.04 nmol/ mg/min		
9,000 g supernatant (contain 5-7 mg protein)						1.43 nmol/ mg/min		
microsome						1.23 nmol/ mg/min		
50 umol bromoform incubated with liver microsomes	Rats	carbon monoxide				Liver microsomes 145.54 nmol/mg protein formed		Stevens JL et al. 1979

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
26 mM bromodichloromethane incubated with liver microsome in an NADPH-generating system		carbon monoxide				Liver microsomal fraction 0.04 nmol/mg/min (enzymic) 0.02 nmol/mg/min (nonenzymic)		Ahmed AE et al. 1977
0.5 mg/kg/day bromodichloromethane, gavage, 25 days	Rats	bromodichloromethane	1 ug/l*			Fat 51 ng/g*	*: average of 9 determinations during dosing	Pfaffenberger CD et al. 1979
			1 ug/l**			4 ng/g **	**: average 3 days and 6 days after dosing	
		chloroform	less than 1 ug/l *			less than 1 ng/g *		
			less than 1 ug/l **			less than 1 ng/g **		
5 mg/kg/day bromodichloromethane, gavage, 25 days		bromodichloromethane	23 ug/l*			Fat 1,800 ng/g*		
			1 ug/l**			3 ng/g** (2)		
		chloroform	less than 1 ug/l *			less than 1 ng/g *		
			less than 1 ug/l **			less than 1 ng/g **		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
1 mg/kg/day carbon tetrachloride, gavage, 25 days	Rats	carbon tetrachloride	11 ug/l*			Fat 1,900 ng/g*	*average of 9 determinations during dosing **average 3 days and 6 days after dosing	Pfaffenberger CD et al. 1979
		chloroform	less than 1 ug/l ** less than 1 ug/l * less than 1 ug/l **			14 ng/g** 140 ng/g* (1) 6 ng/g**		
10 mg/kg/day carbon tetrachloride, gavage, 25 days		carbon tetrachloride	310 ug/l*			Fat 18,000 ng/g*		
		chloroform	less than 1 ug/l** 59 ug/l* (1) 16 ug/l**			168 ng/g** 2,600 ng/g* (1) 17 ng/g**		
10 umol carbon tetrachloride and 0.5 ml liver homogenates incubated with:	Rats					Liver homogenates		Shah H et al. 1979
control		carbon dioxide				27 nmol/g		
1.6 mM NADH						373 nmol/g		
1.6 mM NADPH						464 nmol/g		
1.6 mM NADH + NADPH *						472 nmol/g	* no significant additive effect	
10 umol carbon tetrachloride and 0.5 ml liver homogenates incubated with:								
1.6 mM NADPH		carbon dioxide				572 nmol/g		
1.6 mM NADH + NADPH-regenerating system						460 nmol/g		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
10 umol carbon tetrachloride and 0.5 ml liver homogenates incubated with:	Rats							
0 umol formate		carbon dioxide				125 nmol/g		Shah H et al.
1 umol formate						137 nmol/g		1979
10 umol formate						139 nmol/g		(cont.)
10 umol carbon tetrachloride and 0.5 ml liver homogenate incubated with:								
0 umol formate		carbon dioxide				348 nmol/g		
10 umol formate						376 nmol/g		
10 umol carbon tetrachloride and 0.5 ml liver homogenate incubated with:								
0 mol chloroform		carbon dioxide				187 nmol/g		
1 mol chloroform						205 nmol/g		
10 mol chloroform						184 nmol/g		
10 umol carbon tetrachloride and 0.5 ml liver homogenate incubated with:		carbon dioxide						
0 mol chloroform						476 nmol/g		
10 mol chloroform						484 nmol/g		
10 umol carbon tetrachloride and 0.5 ml liver homogenate incubated with:								
0 mM cysteine		carbon dioxide				580 nmol/g		
		acid-soluble fraction				248 nmol/g		
5 mM cysteine		carbon dioxide				510 nmol/ml		
		acid-soluble fraction				578 nmol/ml		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
1 mg/l radioactive-labeled carbon tetrachloride in 50 liters aerated de-chlorinated water at 12°C for 2 hr, then transferred to fresh water	Trout	carbon tetrachloride	6.84 nmol/ml (0 hr) 2.10 nmol/ml (1 hr) 1.69 nmol/ml (2 hr) 0.61 nmol/ml (4 hr) 0.38 nmol/ml (8 hr)			Fat 76.60 nmol/g (0 hr) 91.04 nmol/g (1 hr) 99.60 nmol/g (2 hr) 55.74 nmol/g (4 hr) 47.66 nmol/g (8 hr) Liver 12.78 nmol/g (0 hr) 6.14 nmol/g (1 hr) 5.49 nmol/g (2 hr) 5.20 nmol/g (4 hr) 5.25 nmol/g (8 hr)	Half-life blood: 2.77 hr liver: 38.93 hr heart: 1.99 hr muscle: 1.71 hr gill: 3.20 hr brain: 2.63 hr skin: 3.04 hr spleen: 2.29 hr	Statham CN et al. 1978

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
o-chlorobenzylidene malononitrile, i.v. Dose	Rabbits							Paradowski M 1979
9.1 mg/kg		o-chlorobenzaldehyde*	450 nmol/cc* 140 nmol/cc				Half-life in blood: 0.31 min	
		o-chlorobenzyl malononitrile	85 nmol/cc* 37 nmol/cc				* Liver excluded from circulation	
13.7 mg/kg							Half-life in blood: 0.41 min	
18.3 mg/kg		o-chlorobenzaldehyde + malononitrile	500 nmol/cc				Half-life in blood: 0.38 min	
8.5 mg/kg (LD50/24 hr) o-chlorobenzaldehyde, i.v.							Half-life in blood: 0.69 min	
38.8 mg/kg (LD50/24 hr) o-chlorobenzylmalononitrile, i.v.							Half-life in blood:	
424 umol/kg (LD50/24 hr) malononitrile, i.v.			5300 nmol/cc					

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
300 mg 1-chloronaphthalene in solution, 2 min retrocarotid injection	Pigs	1-chloro-naphthalene	5.1 ug/g (10 min) 3.4 ug/g (20 min) 1.8 ug/g (40 min) 0.7 ug/g (80 min) 0.9 ug/g (120 min) 0.3 ug/g (160 min) 0.3 ug/g (200 min) 0.1 ug/g (240 min)			Brain 6.7 ug/g (6 hr) Kidney 16.1 ug/g (6 hr) Liver 2.3 ug/g (6 hr) Lung 1.0 ug/g (6 hr) Heart 1.5 ug/g (6 hr) Psoas 5.0 ug/g (6 hr) Skeletal muscle 1.0 ug/g (6 hr)		Ruzo LO et al. 1976
		4-chloronaphthol	0.1 ug/g (160 min) 0.6 ug/g (200 min) 0.8 ug/g (240 min) 1.0 ug/g (260 min) 1.3 ug/g (300 min)		440.0 ug/g	Kidney 1.4 ug/g (6 hr) Liver 1.0 ug/g (6 hr) Bile 900 ug/g (6 hr)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
300 mg 2-chloronaphthalene in solution, 2 min retrocarotid injection		2-chloro-naphthalene	6.2 ug/g (10 min) 3.8 ug/g (20 min) 1.9 ug/g (40 min) 1.0 ug/g (80 min) 1.0 ug/g (120 min) 0.6 ug/g (160 min) 0.2 ug/g (200 min) 0.2 ug/g (240 min) 0.1 ug/g (260 min)			Brain 21.4 ug/g (6 hr) Kidney 14.4 ug/g (6 hr) Fat 0.6 ug/g (6 hr) Liver 5.2 ug/g (6 hr) Lung 0.8 ug/g (6 hr) Heart 4.5 ug/g (6 hr) Psoas 4.5 ug/g (6 hr) Skeletal muscle 2.2 ug/g (6 hr)		Ruzo LO et al. 1976 (cont.)
		3-chloro-2-naphthol	0.2 ug/g (200 min) 0.5 ug/g (240 min) 0.8 ug/g (260 min) 1.0 ug/g (300 min)		60.0 ug/g (6 hr)	Kidney 0.6 ug/g (6 hr) Liver 0.7 ug/g (6 hr) Bile 260.0 ug/g (6 hr)		

Chloronaphthalene (Continued)

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
400 mg/kg 1,2-dichloronaphthalene, single oral	Rats	5,6-dichloro-1,2-dihydroxy-1,2-dihydronaphthalene (glucuronide conjugate)			identified			Secours V et al. 1977
400 mg/kg 2,7-dichloronaphthalene, single oral		7-chloro-2-naphthol (free + conjugated)				identified		
400 mg/kg 2,6-dichloronaphthalene, single oral		6-chloro-2-naphthol (free + conjugated)				identified		
		2,6-dichloronaphthol				identified		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
26 mM chloroform incubated with liver microsome in an NADPH-generating system	Rats	carbon monoxide				Liver microsomal fraction 0.00 nmol/mg/0.03 nmol/mg/min (enzymic) min (nonenzymic)		Ahmed AE et al. 1977
1.75 nmol radioactive labelled chloroform, sacrificed 3 hr after administration	Mice					Liver* MP: 101 ML: 129 EP: 115 EL: 154 CP: 234 Kidney* MP: 117 ML: 211 EP: 191 EL: 165 CP: 75	MP: mitochondria protein ML: mitochondria lipid EP: endoplasmic reticulum protein EL: endoplasmic reticulum lipid CP: cytosolic protein * specific activity in dpm/mg	Kluwe WM 1979
0.5 mg/kg/day chloroform, gavage, 25 days	Rats	chloroform	12 ug/l* 7 ug/l**			Fat 99 ng/g* 5 ng/g**	*: average of 9 determinations during dosing **: average 3 days and 6 days after dosing	Pfaffenberger CD et al. 1979
5 mg/kg/day chloroform, gavage, 25 days		chloroform	69 ug/l* 8 ug/l** (2)			Fat 12,000 ng/g* 2 ng/g**		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
liver microsomes from i.p. phenobarbital pretreated rats incubated in an atmosphere of air with:	Rats							Pohl LR et al. 1978
1 mM chloroform, 1 mM cysteine		phosgene				Liver microsome 1.98 nmol/mg protein/10 min		
1 mM chloroform, 2 mM cysteine						4.38 nmol/mg protein/10 min		
1 mM deuterium labelled chloroform, 2 mM cysteine						2.29 nmol/mg protein/10 min		
1 mM $(^{14}C)_{chloroform}$ incubated with liver microsomes from i.p. phenobarbital (80 mg/kg) pretreated rats	Rats	$(^{14}C)_{chloroform}$				Liver microsome protein binding 2178 pmole/mg protein/10 min		Pohl LR et al. 1977
1 mM $(^{14}C)_{chloroform}$ 2 mM cysteine incubated with liver microsomes from i.p. phenobarbital (80 mg/kg) pretreated rats		$(^{14}C)_{chloroform}$				Liver microsome protein binding 1032 pmol/mg protein/10 min		
		2-oxothiazolidine-4-carboxylic acid				identified		
1 mM chloroform, 2 mM liver microsomes from i.p. phenobarbital (80 mg/kg) pretreated rats incubated in an $(18O)O_2$ atmosphere		phosgene				identified		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
26 mM dibromochloromethane incubated with liver microsomes in an NADPH-generating system	Rats	carbon monoxide				Liver microsomal fraction 0.42 nmol/ mg/min (enzymic) 0.03 nmol/mg/min (nonenzymic)		Ahmed AE et al. 1977

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
1000 ppm $^{(14C)}$p-dichlorobenzene, inhalation, 3 hr/day, 10 days	Rats	p-dichlorobenzene	0.2%		73.0% (0-24 hr) 19.8% (24-48 hr) 3.4% (48-72 hr) 0.8% (72-96 hr) 0.4% (96-120 hr) 97.4% (total) 51.5%*	Feces 2.5% (0-24 hr) less than 0.1% (24-120 hr) 2.5% (total) Bile 48.5%*	time intervals after dosing ceased * rats with cannulated bile ducts	Hawkins DR et al. 1980
		2,5-dichlorophenyl sulfate 2,4-dichlorophenyl glucuronide unknown			54% (24 hr) 34% (24 hr) 10% (24 hr)			
250 mg/kg/day $^{(14C)}$p-dichlorobenzene, oral, up to 10 days		p-dichlorobenzene		1.0%	87.0% (0-24 hr) 7.5% (24-48 hr) 2.5% (48-72 hr) 0.1% (72-96 hr) less than 0.1% (96-120 hr) 97.1% (total)	Feces 1.9% (0-24 hr) 0.1% (24-48 hr) less than 0.1% (48-120 hr) 2.0% (total) Bile 63.0%*		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
					28.1%*			Hawkins DR et al. 1980 (cont.)
		2,5-dichlorophenyl sulfate			46% (0-24 hr)			
		2,4-dichlorophenyl glucuronide			33% (0-24 hr)			
		unknown			10% (0-24 hr)			
250 mg/kg/day $^{(14C)}$p-dichlorobenzene, subcutaneous, up to 10 days		p-dichlorobenzene		6.4%	41.0% (0-24 hr) 23.5% (24-48 hr) 13.5% (48-72 hr) 7.8% (72-96 hr) 4.7% (96-120 hr) 90.5% (total)	Feces 0.1% (0-24 hr) 0.9% (24-48 hr) 0.9% (48-72 hr) 0.6% (72-96 hr) 0.6% (96-120 hr) 3.1% (total)		
					54.0%*	Bile 46.0%*		
		2,5-dichlorophenyl sulphate			53% (0-24 hr)			
		2,4-dichlorophenyl glucuronide			31% (0-24 hr)			
		unknown			7% (0-24 hr)			
2.63 mg/m^3 p-dichlorobenzene in Tokyo ambient air	Pigeons*	p-dichlorobenzene				Adipose 1.85 ppm	*from environment	Morita M et al. 1978
	Humans					1.88 ppm		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
750 mg/kg 1,2-dichloroethane, single oral	Rats	chloroethanol	5.6 ug/ml (1 hr) 67.8 ug/ml (4 hr) 37.6 ug/ml (12 hr) 14.1 ug/ml (24 hr) 8.2 ug/ml (48 hr)			Liver 0.5 ug/g (12 hr) 13.5 ug/g (24 hr) 13.0 ug/g (48 hr)		Kokarovtseva MG et al. 1978
255 umol 1,2-dichloroethane incubated with 6 mg cytosol protein, 30 umol GSH, 50 umol phosphate buffer	Rats	ethylene				Liver 10.3 pmol/min/mg Kidney 5.2 pmol/min/mg		Livesey JC et al. 1979
15 mg/kg 1,2-dichloroethane, i.v.	Rats	1,2-dichloroethane				Fat* 24.92 ug/g	* peak concentration Maximal accumulation in fat: 32.5 min Elimination half-life in fat: 78 min	Withey JR et al. 1980

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
(2-^{14}C)1,1-dichloroethylene	Rats						percentages of administered dose	Jones BK et al. 1978
Intragastric dose						Feces		
500 ug/kg		1,1-dichloro-ethylene		0.6% (0-24 hr)	71.3% (0-24 hr)	5.1% (0-24 hr)		
				0.06% (24-48 hr)	5.3% (24-48 hr)	2.7% (24-48 hr)		
				0.08% (48-72 hr)	3.6% (48-72 hr)	0.6% (48-72 hr)		
				0.7% (total)	80.2% (total)	8.3% (total)		
		carbon dioxide		3.9% (0-24 hr)				
				0.5% (24-48 hr)				
				0.5% (48-72 hr)				
				4.8% (total)				
						Feces		
350 mg/kg		1,1-dichloro-ethylene		62.4% (0-24 hr)	17.6% (0-24 hr)	0.4% (0-24 hr)		
				4.8% (24-48 hr)	10.0% 24-48 hr)	0.5% (24-48 hr)		
				0.1% (48-72 hr)	1.9% (48-72 hr)	0.4% (48-72 hr)		
				67.3% (total)	29.5% (total)	1.3% (total)		
		carbon dioxide		0.3% (0-24 hr)				
				0.4% (24-48 hr)				
				0.3% (48-72 hr)				
				1.0% (total)				
I.V. dose						Feces		
500 ug/kg		1,1-dichloroethylene		80% (0-24 hr)	14.4% (0-24 hr)	0.3% (0-24 hr)		
				0% (24-48 hr)	0.7% (24-48 hr)	0.1% (24-48 hr)		
				0% (48-72 hr)	0% (48-72 hr)	0% (48-72 hr)		
				80% (total)	15.0% (total)	0.4% (total)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
		carbon dioxide		3.5% (0-24 hr) 0% (24-48 hr) 0% (48-72 hr) 3.5% (total)				Jones BK et al. 1978 (cont.)
I.P. dose 500 ug/kg		1,1-dichloro-ethylene		11.4% (0-24 hr) 0.2% (24-48 hr) 0.1% (48-72 hr) 11.7% (total)	65.8% (0-24 hr) 2.0% (24-48 hr) 1.2% (48-72 hr) 69.0% (total)	Feces 14.2% (0-24 hr) 1.6% (24-48 hr) 0.4% (48-72 hr) 16.2% (total)		
		carbon dioxide		2.6% (0-24 hr) 0.5% (24-48 hr) 0.5% (48-72 hr) 3.6% (total)				
350 ug/kg		1,1-dichloro-ethylene		90.5% (0-24 hr) 0.6% (24-48 hr) 0% (48-72 hr) 91.1% (total)	7.1% (0-24 hr) 0.3% (24-48 hr) 0.3% (48-72 hr) 7.7% (total)	Feces 0.5% (0-24 hr) 0.1% (24-48 hr) 0.1% (48-72 hr) 0.7% (total)		
		carbon dioxide		0.7% (0-24 hr) 0.5% (24-48 hr) 0.1% (48-72 hr) 1.3% (total)				

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
350 mg/kg ($1^{14}C$)1,1-dichloroethylene, intragastric		1,1-dichloroethylene			0% (0-3 hr) 2.9% (3-6 hr) 15.8% (6-24 hr) 3.1% (24-48 hr)		percentage of administered radioactivity	Jones BK et al. 1978 (cont.)
		thiodiglycollic acid			37.0%			
		N-acetyl-S-cysteinyl-acetyl derivative			48.0%			
		dithioglycollic acid			5.0%			
		thioglycollic acid			3.0%			
		chloroacetic acid			3.0%			
		urea			0.5%			
		S-(carboxymethyl)-cysteine			0%			
350 mg/kg ($1^{14}C$-)-1,1-dichloroethylene, intragastric Rat equipped with biliary fistula		1,1-dichloroethylene			0% (0-3 hr) 0.2% (3-6 hr) 6.5% (6-24 hr) 2.4% (24-48 hr)	Bile 0.9% (0-3 hr) 2.1% (3-6 hr) 5.9% (6-24 hr) 2.4% (24-48 hr)		
0.5 mg/kg (^{14}C) 1,1-dichloroethylene, single oral	Rats	1,1-dichloroethylene (unchanged)		0.9%	52%		percentage of administered radioactivity	Reichert D et al. 1978
		carbon dioxide		23%				
50 mg/kg (^{14}C)1,1-dichloroethylene, single oral		1,1-dichloroethylene (unchanged)		20%	36%			
		carbon dioxide		6%				
0.5 mg/kg (^{14}C)1,1-dichloroethylene, stomach tube	Rats	1,1-dichloroethylene (unchanged)		1.26% (0-72 hr)	43.55% (0-72 hr)	Fecal 15.74% (0-72 hr)	percentage of administered radioactivity	Reichert D 1979

1,1-Dichloroethylene (Continued)

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
		carbon dioxide		13.64% (0-72 hr)				Reichert D 1979 (cont.)
5.0 mg/kg (^{14}C)1,1-dichloroethylene, stomach tube		1,1-dichloroethylene (unchanged)		9.70% (0-72 hr)	53.88% (0-72 hr)	Fecal 14.54% (0-72 hr)		
		carbon dioxide		11.35% (0-72 hr)				
50 mg/kg (^{14}C)1,1-dichloroethylene, stomach tube		1,1-dichloroethylene (unchanged)		16.47% (0-72 hr)	42.11% (0-72 hr)	Fecal 7.65% (0-72 hr)	Main urinary metabolites identified thiodiglycolic acid N-acetyl-S-(2-carboxymethyl) cysteine and methylthio-acetyl-aminoethanol	
		carbon dioxide		6.13% (0-72 hr)				

1,2-Dichloropropane

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
20 mg/kg 1,2-dichloropropane, oral, 4 days	Rats	N-acetyl-S-(2-hydroxypropyl) cysteine			25-35%			Jones AR et al. 1980
		N-acetyl-S-(2,3-dihydroxypropyl)-cysteine			identified			
		beta-chlorolactate			identified			
100 mg/kg 1,2-dichloroethane, single i.p.		1,2-dichloro-propane (unchanged)		5% (0-3 hr) 5% (9-18 hr)				

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
1.42 mM ^{14}C-hexachlorobenzene/kg, i.p.	Rats					Feces	percentage of radioactivity	Koss G et al. 1978
		hexachlorobenzene			1% (0-4 wk)	69% (0-4 wk)		
		pentachlorophenol			28% (0-4 wk)	16% (0-4 wk)		
		pentachlorothiophenol			46% (0-4 wk)	9% (0-4 wk)		
		tetrachlorohydroquinone			17% (0-4 wk)	0% (0-4 wk)		
		tetrachlorothiophenol			1% (0-4 wk)	0% (0-4 wk)		
no occupational exposure to chlorinated hydrocarbons	Humans (9)	hexachlorobenzene	1.04 ppb				numbers of subjects in parentheses	Lunde C et al. 1977
polyvinyl chloride plant workers	(9)	hexachlorobenzene	1.54 ppb					
magnesium plant workers	(17)	hexachlorobenzene	29.61 ppb					
technical grade pentachlorophenol (20 mg/kg/day for day 1-42; 15 mg/kg/day for day 43-160), oral (diet)	Heifers (12)						hexachlorobenzene is a contaminant	Parker CE et al. 1980
Technical grade pentachlorophenol in dose								
0%			0.16 ppb (day 160)					
10%			0.25 ppb (day 160)					
35%			0.46 ppb (day 160)					
100%			0.77 ppb (day 160)					
300 mg/kg hexachlorobenzene, oral	Rats	2,4,5-trichlorophenol			identified			Renner G et al. 1977

Hexachlorobenzene (Continued)

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
110 ug ^{14}C-hexachlorobenzene, oral (diet), up to 550 days	Monkeys	hexachlorobenzene pentachlorobenzene pentachlorophenol pentachloro--benzene, hexa-chlorobenzene, and tetrachloro-benzene			50-75% 25-50%	Feces 99% approx. 1% trace		Rozman K et al. 1978
300 ppm technical grade pentachloronitrobenzene (impurities: 0.21 ppm pentachlorobenzene, 0.6 ppm 2,3,4-tetrachloronitrobenzene, 4.5 ppm hexachlorobenzene), oral (diet), 16 weeks	Hens	hexachlorobenzene	0.403 ppm			Fat 19.8 ppm Bile-gall bladder 17.50 ppm Liver 7.47 ppm Egg yolk 7.95 ppm Egg white 0.032 ppm Breast muscle 0.334 ppm Excreta not detect-able	Half-life: 90 days	Simon GS et al. 1979
1.3 uCi ^{14}C-hexachlorobenzene, i.v.	Rats	hexachlorobenzene			0.2%	Feces 1% Fat approx. 0.3 ug eq/g	percentage of administered dose	Yang RSH et al. 1978
12.9 uCi ^{14}C-hexachloro-benzene, i.v.	Monkeys	hexachlorobenzene			1.6% (6 yr)	Feces 28.2% (1 yr)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
						Fat S: 430.5 ng/g (1 yr) O: 397.8 ng/g (1 yr) Bone marrow 372.6 ng/g (1 yr) Adrenal gland 72.5 ng/g (1 yr)	S: subcutaneous fat O: omental fat	Yang RSH et al. 1978 (cont.)
24.7 uCi ^{14}C-hexachlorobenzene, i.v.		hexachlorobenzene			1.8% (100 day)	Feces 17.1% (100 day) Fat S: 3170.3 ng/g (100 day) O: 2899.1 ng/g (100 day) Adrenal gland 367.5 ng/g (100 day)		
26.2 uCi ^{14}C-hexachlorobenzene, i.v.		hexachlorobenzene			1.1% (3 mo)	Feces 8.8% (6 mo) Fat S: 1829.8 ng/g (6 mo) O: 1789.9 ng/g (6 mo) Bone marrow 1637.8 ng/g (6 mo) Adrenal gland 328.7 ng/g (6 mo)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
hexachloroethane, oral (diet), 110 days	Rats						Half-life in kidney: 2-3 days	Gorzinsky SJ et al. 1979
Dose						Kidney		
1.5 mg/kg/day		hexachloroethane				1.4 ug/g (male) 0.4 ug/g (female)		
20 mg/kg/day						24.3 ug/g (male) 0.7 ug/g (female)		
80 mg/kg/day						95.1 ug/g (male) 2.0 ug/g (female)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
0.025 mCi/mmol (^{14}C)-methylene chloride incubated with liver microsomes	Rats						* covalent binding to microsome (nmol bound/mg protein or lipid/min)	Anders MV et al. 1977
Pretreatment						Liver microsome*		
control		methylene chloride				lipid: 0.27 protein: 0.14		
50 mg/kg phenobarbital i.p.						lipid: 1.97 protein: 0.57		
2,600 mg/m^3 methylene chloride (750 ppm), inhalation, 1 hr while exercising at a rate of 50 W on a bicycle ergometer	Humans (12 male)	methylene chloride				Adipose* 10.2 mg/kg (1 hr) 8.4 mg/kg (4 hr)	* mean concentration	Engstrom J et al. 1977
methylene chloride, closed rebreathing system	Rats					Concentration in closed system		Rodkey FL et al. 1977a
Dose (umol/kg)								
82		carbon monoxide*				0.46 (4 hr)**	* per mole methylene chloride administered	
100						0.48 (4 hr)**		
122						0.48 (4 hr)**	**moles CO produced per mole of methylene chloride given	
793						0.18 (4 hr)**		
0.2 mmol/kg methylene chloride (.75 uCi/kg), closed rebreathing system, sacrificed after 7 hr	Rats	carbon monoxide		46.9%				Rodkey FL et al. 1977b
		carbon dioxide		28.9%				

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
0.024 mg/l ^{14}C-pentachloroanisole, 12 hr, transferred to fresh water	Rainbow Trout	pentachloroanisole					Elimination half-life liver: 6.9 days fat: 23.4 days muscle: 6.3 days blood: 6.3 days	Glickman AH et al. 1977
0.024 mg/l ^{14}C-pentachloroanisole, 24 hr, transferred to fresh water		pentachlorophenol					Elimination half-life liver: 9.8 hr fat: 23.7 hr muscle: 6.9 hr	
0.05 mg/l ^{14}C-pentachloroanisole, 12 hr		pentachlorphenol-glucuronide pentachlorophenol pentachloroanisole				Bile 257 ng (83%) 6 ng (2%) 47 ng (15%)		
0.05 mg/l, ^{14}C-pentachloroanisole 12 hr after being in 1 mg/l 24 hr		pentachlorophenol-glucuronide pentachlorophenol pentachloroanisole				Bile 85 ng (42%) 10 ng (5%) 107 ng (53%)		
20 mg/kg ^{14}C-pentachloroanisole, single i.p.	Mice	pentachlorophenol (free) tetrahydroquinone			2% 17%	Feces 32% 6%	Elimination half-life blood: 5.6 hr urine: 5.6 hr feces: 8.0 hr liver: 19.3 hr muscle: 6.1 hr adipose: 7.0 hr skin: 6.2 hr	Vodnick MJ et al. 1980

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
403 uM pentachlorobenzene, i.p.	Rats	pentachlorobenzene (unchanged) pentachlorophenol				Urine & Feces 3% 9%	Other metabolites 2,3,4,5-tetra-chlorophenol tetrachlorohydro quinone hydroxylated chlorothio compound tetrachlorophenol isomer	Koss G et al. 1978
20 mg pentachlorobenzene, single oral	Monkeys	pentachlorobenzene				Urine & Feces 22% (0-6 days)	metabolites identified in urine: 2 isomers of tetrachlorophenol	Leber AP et al. 1977
no occupational exposure to chlorinated hydrocarbons	Humans (9)	pentachlorobenzene	*				number of subjects in parentheses	Lunde G et al. 1977
polyvinyl chloride plant workers	(9)		*				* no data	
magnesium plant workers	(17)		0.15 ppb					
300 ppm technical grade pentachloronitrobenzene* oral (diet), 16 weeks * contains 0.21 ppm penta-chlorobenzene, 0.6 ppm tetrachlorobenzene, 4.5 ppm hexachlorobenzene	Hens	pentachlorobenzene	0.013 ppm			Fat 1.32 ppm Bile-gall bladder 1.46 ppm Liver 0.276 ppm Egg yolk 0.355ppm Egg white 0.007 ppm		Simon GS et al. 1979

Pentachlorobenzene (Continued)

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
						Breast muscle 0.013 ppm Excreta 0.015 ppm		Simon GS et al. 1979 (cont.)

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
5 mg/kg/day 1,2,4,5-tetrachlorobenzene, oral (diet), 2 yr	Beagle Dogs	tetrachlorobenzene					Uptake rate constants blood: very large fat: very large Elimination rate constants blood: 6.64×10^{-3}/day fat: 6.01×10^{-3}/day Half-life blood: 104 days fat: 111 days	Braun WH et al. 1978
tetrachlorobenzene in Norway fjord	Fish	tetrachlorobenzene				Fat 0.08-1.4 ppm		Ofstad EB et al. 1978

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
3.3 uM tetrachloroethylene incubated with hepatic microsome	Rats							Costa AK et al. 1980
Additions						Spectral binding to cytochrome P-450		
None		tetrachloro-ethylene				100%		
		trichloroacetate				100%		
200 mM SKF525A		tetrachloro-ethylene				81%		
		trichloroacetate				67%		
2.33 mM metyrapone		tetrachloro-ethylene				20%		
		trichloroactate				25%		
$CO:O_2$ (80:20)		tetrachloro-ethylene				not determined		
		trichloroacetate				25%		
eels in 50 ppm tetrachloro-ethylene solution for 3 days; their flesh removed and homogenized with water (20.5 ppm tetrachloroethylene); 10 ml/kg homogenized solution, oral	Rats	tetrachloro-ethylene	24.8 ng/g (3 hr) 19.6 ng/g (6 hr) 13.1 ng/g (12 hr) 11.5 ng/g (20 hr)			Liver 160.0 ng/g (3 hr) 55.5 ng/g (6 hr) 23.3 ng/g (12 hr) 18.5 ng/g (20 hr) Adipose tissue 104.3 ng/g (3 hr) 248.2 ng/g (6 hr) 141.8 ng/g (12 hr) 55.9 ng/g (20 hr)	Half-life blood : 16 hr liver : 5 hr adipose tissues : 6 hr	Miyake Y 1978

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
						Kidney 25.9 ng/g (3 hr) 35.1 ng/g (6 hr) 42.1 ng/g (12 hr) 114.1 ng/g (20 hr) Muscle 28.3 ng/g (3 hr) 22.4 ng/g (6 hr) 19.3 ng/g (12 hr) 13.2 ng/g (20 hr)		Miyake Y 1978 (cont.)
70 ppm tetrachloroethylene, inhalation, 4 hr	Humans (4-6)	tetrachloroethylene trichloroacetic acid			95%			Monster AC 1979
1 mg/kg tetrachloroethylene, oral gavage, sacrificed after 72 hr	Rats	carbon dioxide tetrachloro-ethylene		0.04 umol eq (2.5%) 1.05 umol eq (71.5%)	 0.24 umol eq (16.5%)	 Feces 0.09 umol eq (6.2%) Carcass 0.05 umol eq (3.3%)		Pegg DG et al. 1979
500 mg/kg tetrachloroethylene, oral gavage, sacrificed after 72 hr		carbon dioxide tetrachloro-ethylene		3.44 umol eq (0.5%) 667.31 umol eq (89.9%)	 34.48 umol eq (4.6%)	 Feces 29.08 umol eq (3.9%)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
						Carcass 8.5 umol eq (1.2%)		Pegg DG et al. 1979 (cont.)
10 ppm tetrachloroethylene, inhalation, 72 hr		carbon dioxide		0.32 umol eq (3.6%)				
		tetrachloro-ethylene		6.08 umol eq (68.1%)	1.66 umol eq (18.7%)	Feces 0.46 umol eq (5.2%)		
						Carcass 0.38 umol eq (4.3%)		
600 ppm tetrachloroethylene, inhalation, 72 hr		carbon dioxide		3.25 umol eq (0.7%)				
		tetrachloro-ethylene		412.38 umol eq (88%)	27.40 umol eq (6.0%)	Feces 14.24 umol eq (3.1%)		
						Carcass 10.07 umol eq (2.2%)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
0.018 mg/l (14C)-1,2,4-trichlorobenzene, 8 hr static exposure; transferred to fresh flowing water	Trout	^{14}-C label	33*			Liver 102* Muscle 51* Bile 104-240*	* maximal ratio: tissue/water Elimination half-lives for days 1-2 blood: 0.02 days liver: 0.4 days muscle: 0.4 days	Melancon MJ et al. 1980
0.020 mg/l (14C)-1,2-4-trichlorobenzene, continuous flow, 35 days; transferred to fresh flowing water		^{14}-C label	84*			Liver 389* Bile 500-1400* Muscle 89*	Elimination half-lives for days 4-36 liver: 56 days muscle: 47 days blood: less than 1 day	
0.40 mg/l (14C)-1,2,4-trichlorobenzene, 24 hr		^{14}-C label	5.8 ug/ml			Bile 38.2 ug/g Muscle 9.6 ug/g Liver 19.3 ug/g		
0.24 mg/l (14C)-1,2,4-trichlorobenzene, 24 hr		^{14}-C label	1.3 ug/ml			Bile 6.8 ug/g Muscle 2.5 ug/g Liver 4.0 ug/g Kidney 1.8 ug/g Plasma 1.4 ug/g		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
0.20 mg/l (14C)-1,2,4-trichlorobenzene, 24 hr	Carp	^{14}-C label	2.8 ug/ml			Bile 18.1 ug/g Muscle 2.2 ug/g Liver 11.3 ug/g Kidney 7.6 ug/g Plasma 3.0 ug/g		Melancon MJ et al. 1980 (cont.)
1 mmol/kg/day (14C)-1,2,4-trichlorobenzene, oral, 7 days	Rats	^{14}-C label			72% (day 1-15)	Feces 4% (day 1-8) Abdominal fat 2033 dpm/g (day 1) 642 dpm/g (day 6) 342 dpm/g (day 11) 408 dpm/g (day 16) Liver 1075 dpm/g (day 1) 442 dpm/g (day 6) 308 dpm/g (day 11) 317 dpm/g (day 16) Adrenal gland 754 dpm/g (day 1) 246 dpm/g (day 6)	post exposure amount 6,660,000 dpm total	Smith E et al. 1980

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
						Muscle 400 dpm/g (day 1) Kidney 1471 dpm/g (day 1) 404 dpm/g (day 6) Heart 438 dpm (day 1) Spleen 404 dpm (day 1)		Smith E et al. 1980 (cont.)

1,1,1-Trichloroethane

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
70 ppm 1,1,1-trichloroethane, inhalation, 4 hr	Humans (6)	trichloroethanol			less than 2%		half life in blood: 10-12 hr	Monster AC 1979
		trichloroacetic acid			less than 2%		half life in blood: 80-100 hr	
		trichloroethane (unchanged)		80%			half life for adipose saturation: 25 hr	
							blood/gas partition coefficient = 5	

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
100 umol ^{14}-C trichloroethylene, i.p., sacrificed after 4 hr	Rats	trichloroethylene				Muscle* 3.1 nmol/g Liver* 117 nmol/g	* amount bound to tissue proteins	Allemand H et al. 1978
100 umol ^{14}-C trichloroehtylene i.p. to phenobarbital pretreated		trichloroethylene				Muscle* 4.1 nmol/kg Liver* 171 nmol/kg		
5 umol ^{14}-C trichloroethylene incubated under air with microsomes from 125 mg of liver and an NADPH generating system Pretreatment control 10 mg/kg phenobarbital i.p. 30 mg/kg $CoCl_2$ s.c.		trichloroethylene				Liver microsomes 7.7** 53.7** 5.5**	** amount (nmol/g liver/15 min) irreversibly bound to microsome proteins	
30-45 ppm trichloroethylene, isolated lung perfusion, 3.5 hr	Rats	trichloroethanol	2.0 ug/g of lung			Lung 1.17 ug/g of lung	trichloroethylene blood/air partition coefficient was 26 for rats, 2 for guinea pigs	Dalbey W et al. 1978
	Guinea Pigs	trichloroethanol trichloroacetic acid				Lung 4.64 ug/g of lung 87.5% (200 min) 12.5% (200 min)		

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
30-45 ppm trichloroethylene, isolated lung perfusion; 75 mg/kg i.p. phenobarbital pretreatment	Rats	trichloroethanol	3.44 ug/g of lung			Lung 93.3% (140 min)		Dalbey W et al. 1978 (cont.)
		trichloroacetic				6.7% (140 min)		
30-45 ppm trichloroethylene, isolated lung perfusion; 35 ul ethanol added 5 min after respiration initiation		trichloroethanol	2.28 ug/g of lung (140 min)					
50 ppm trichloroethylene, intermittent inhalation exposure during 8 hr/day work	Humans (6 males)						Biological half-life in urine trichlorocompounds: 50.7 hr trichloroethanol: 42.7 hr trichloroacetic acid: 57.6 hr	Ikeda M 1977
200 ppm trichloroethylene, intermittent inhalation during 8 hr/day work	Humans (6 females)						Biological half-life in urine trichlorocompounds: 26.1 hr trichloroethanol: 15.3 hr trichloroacetic: acid 39.7 hr	
70 ppm trichloroethylene, inhalation at rest, 4 hr	Humans (6)	trichloroethylene		10%			Half-life in blood trichloroethanol: 10-12 hr trichloroacetic acid: 80-100 hr	Monster AC 1979
		trichloroethanol			43%			
		trichloroacetic acid			21%			

Trichloroethylene (Continued)

Administration Dose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	Breath	Urine	Other (Specify)	Comments	Reference
10 mg trichloroethylene, single i.p. injection	Rats	trichloroethanol			3.18 mg (0-3 day)			Nomiyama H et al. 1979
		trichloroacetic acid			0.26 mg (0-3 day)			
		total trichloro-compounds			3.73 mg (0-3 day)			
0.5 g trichloroethylene, single i.p. injection	Rabbits	trichloroethanol			157.2 mg (0-4 day)			
		trichloroacetic acid			0.9 mg (0-4 day)			
		total trichloro compounds			172.7 mg (0-4 day)			
1 mg/kg/day trichloroethylene, gavage, 25 days	Rats	trichloroethylene	1 ug/l*			Fat 280 ng/g*	*: average of 9 determinations **: average 3 days and 6 days after dosing	Pfaffenberger CD 1979
			1 ug/l**			1 ng/g**		
		chloroform	1600 ug/l*			100 ng/g*		
			28 ug/l**			6 ng/g**		
10 mg/kg day/trichloroethylene, gavage, 25 days		trichloroethylene	1 ug/l*			Fat 20,000 ng/g*		
			6 ug/l**			1 ng/g**		
		chloroform	9300 ug/l*			480 ng/g* (1)		
			60 ug/l**			less than 1 ng/g **		

dministration ose, Route, Rate	Species	Metabolite	Level (Time Interval) Blood	 Breath	 Urine	Other (Specify)	Comments	Reference
richloroethylene, ontinuous inhalation Day (ppm) 1 41 2 26 3 26 1 40 2 35 3 39	Humans (2) Volunteer #1 Volunteer #2	trichloroacetic acid			54 mg/l 51 mg/l 61 mg/l 97 mg/l 67 mg/l 92 mg/l		ratio of tri- chloroethylene retained to tri- chloroacetic acid excreted per day was approximately 1:0.1	Smith CF 1978
100-200 ppm trichloroethylene, inhalation at rest and at work Average uptake Group I: 45% Group II: 44% Group III: 42%	Humans Group I	trichloroacetic acid trichloroethanol	0.4 mg/kg (30 min) 0.7 mg/kg (30 min)		3.0 umol (0-5 hr) 135 umol (0-5 hr)			Vesterberg O et al. 1976
	Group II Group III	trichloroacetic acid trichloroethanol trichloroacetic acid trichloroethanol	0.6 mg/kg (30 min) 0.8 mg/kg (30 min) 0.7 mg/kg (30 min) 1.4 mg/kg (30 min)		9 umol (0-5 hr) 235 umol (0-5 hr) 4 umol (0-5 hr) 344 umol (0-5 hr)			

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This report is the second update of the original EPA report "Metabolism Summaries of Selected Halogenated Organic Compounds in Human and Environmental Media, Literature Survey" (EPA-560/6-79-008).

This report updates available data from 1978 - 1980 on 23 halogenated hydrocarbons (HHC's) identified as environmental pollutants and potential health hazards, including two chemicals not covered in the earlier reports. Included is information on the uptake and retention of the compounds, their subsequent distribution and elimination patterns, the identification and observed concentrations of metabolites, and the metabolic pathways involved. This report includes, as an appendix, a tabular summary of the experimental data reported.

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