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

Metabolism Summaries of Selected Halogenated Organic Compounds in Human and Environmental Media, A Literature Survey

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Introduction

The Office of Program Integration and Information's Survey and Analysis Division is currently conducting a preliminary assessment of halogenated organic compounds in human and environmental media. This effort was undertaken 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.

The major thrust of this preliminary assessment is a comprehensive and systematic analysis of selected halocarbons in man and the environment being conducted under contract by the Research Triangle Institute (RTI). Conceptually, the program may be partitioned into three primary levels as depicted in Figure 1[1]. This schematic flow diagram illustrates the interlocking relationships between the environment and man and their potential association with the incidence of disease, specifically cancer.

The three program levels in Figure 1 represent: (1) the demonstration for man of a halocarbon dosage through environmental exposure via routes such as air, water and food; (2) the demonstration of a body-burden in man through the examination of urine, breath, blood, and tissues for halogenated hydrocarbons; and (3) the demonstration of an association (i.e., a response) between body-burden and the incidence of cancer.

To complement the RTI effort, Tracor-Jitco, Inc., under contract to the Survey and Analysis Division, has conducted a literature survey on the metabolism of selected halocarbons for use in evaluating the human body burden associated with environmental exposure. Forty-nine halogenated hydrocarbons (HHC's) were selected for this metabolism review based on the following information (details of the HHC selection process will be included in the report produced by RTI):

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.

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1 Pellizzari, Edo. Preliminary Assessment of Halogenated Organic Compounds in Man and Environmental Media. Comprehensive Monthly Technical Progress Report No. 16 (February 1979).

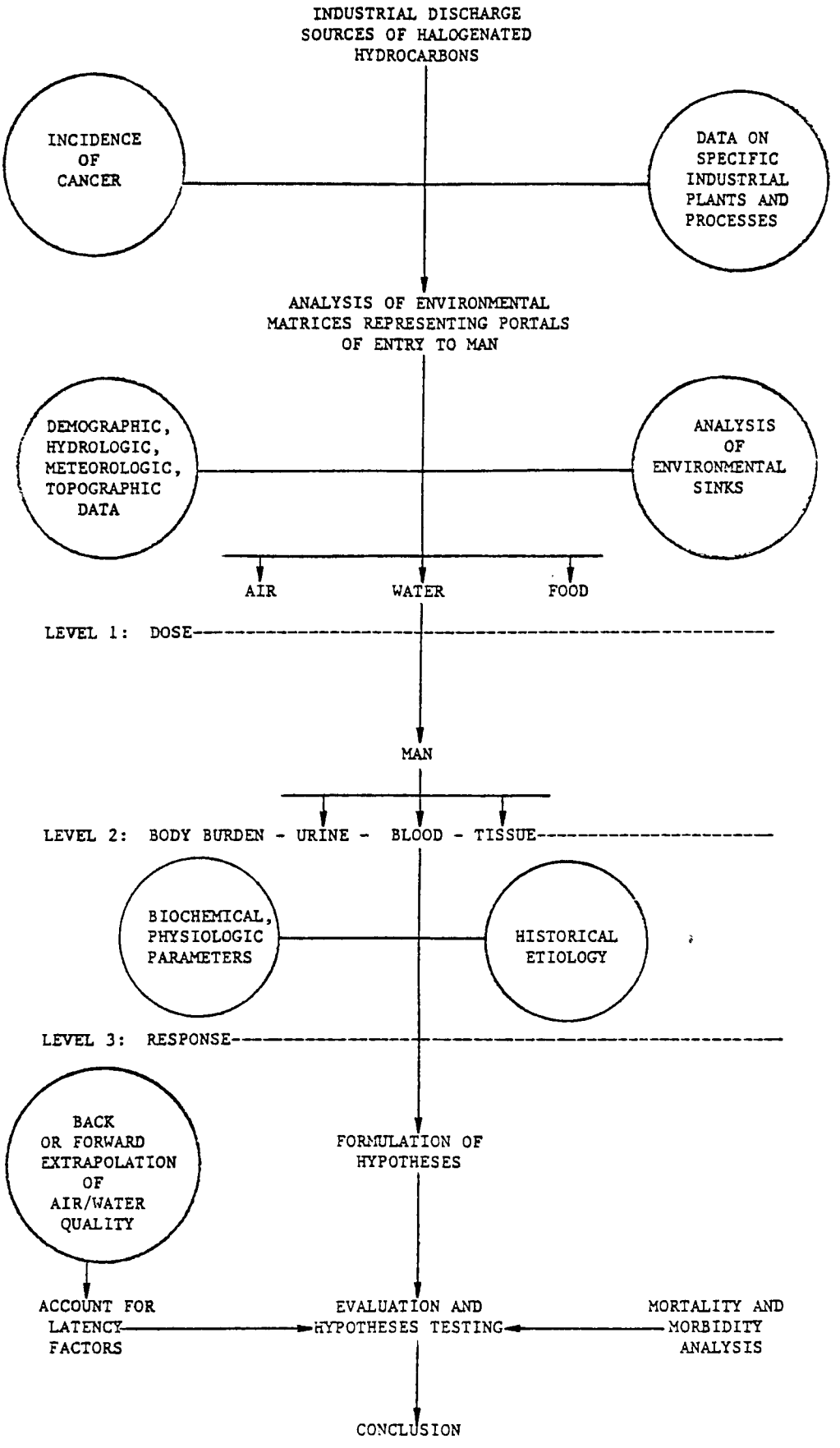
INDUSTRIAL DISCHARGE SOURCES OF HALOGENATED HYDROCARBONS
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Figure 1

The health-related effects associated with many of these chemicals have been studied extensively and are fairly well documented. However, the metabolism of these compounds and the possible toxic effects of their metabolites have yet to be clearly defined.

A thorough literature search pertinent to the metabolism of the selected HHC's was performed and all available information collected; however, information was found on only 30 of the 49 HHC's. The 19 compounds for which no information was available are the following:

Bis(chloroisopropyl)ether
Bromochlorotoluene
Bromodichloroethane
Bromodichloromethane
Chlorobenzotrifluoride
Chloroprene dimer
Dibromochloromethane
Dichlorotoluene
Dibromochlorobenzaldehyde
Dichlorobutane
1,1-Dichloroethane
Dichloroheptane
Methyl dichlorophenoxyacetate
Methyl trichlorophenoxyacetate
Tetrachlorotoluene
Trichlorobutane
Trichlorohexane
Trichloropentane
Trichlorotoluene

The metabolism summaries for each of the 30 HHC's comprise Section II of this report. Basic information on the physical properties of the compounds is included at the beginning of each summary. Molecular and structural formulas, the Chemical Abstracts Registry (CAS) number, accepted synonyms, molecular weight (mol wt), boiling point (bp), and vapor pressure (vp) are presented in the heading of each summary.[2] 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.

For most of the compounds, the available information was quite limited. In those cases, all of the information was incorporated into the reports. Several of the compounds, however, have been extensively researched; in such cases, the information has been summarized, but not every relevant article cited. Special emphasis was given to those articles reporting the highest

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2 Except where otherwise noted, this information was obtained from the Registry of Toxic Effects of Chemical Substances, 1977, NIOSH, and the CRC Handbook of Chemistry and Physics, 53rd and 56th ed.

observed levels of the compounds and their metabolites in humans and experimental animals.

Appendix A of this report consists of a tabular summary of the experimental data. Appendix B of this report consists of a tabular summary of the levels of parent halocarbon and metabolites identified in blood, breath, and urine. Included with this information are some of the reported metabolic pathways for the various compounds.

Secondary information sources utilized in the literature search include:

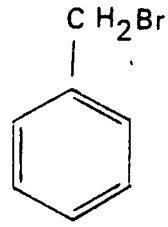
On-Line Data Bases

Agricola
Biosis Previews
CA Condensates
CAB Abstracts
CANCERLINE
Comprehensive Dissertaion Abstracts
Excerpta Medica
NTIS
Scisearch
SSIE
TOXLINE

Abstract Journals

Biological Abstracts
Bioresearch Index
Chemical Abstracts
Excerpta Medica
FDA Clinical Experience Abstracts
Food Science and Technology Abstracts
Occupational Safety and Health Abstracts

BENZYL BROMIDE



C_7H_7Br

CAS: 000100390

Syn: alpha-bromotoluene

Mol. Wt.: 171.05 g/mole

bp: 201°C (at 760 mm Hg)

vp: 1.06 mm Hg (at 25°C)

In a 1958 study conducted by Bray, James and Thorpe (1), rabbits given an aqueous benzyl bromide solution, via stomach tube, were reported to suffer such severe anorexia that many ensuing quantitative tests proved unreliable. Urinalysis was conducted within 24 hours of administration of a 0.2 g/kg body weight dose. Of the original dose, 19% was recovered as mercapturic acid and 2% as ethereal sulfate.

The authors suggested that, due to the high lability of benzyl bromide, "considerable amounts" of the compound may be dehalogenated prior to absorption, resulting in some benzyl alcohol formation (1).

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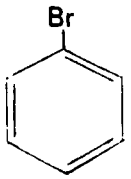
BROMOBENZENE

C_6H_5Br



CAS: 000108861

Syn: phenyl bromide

Mol wt: 157.02 g/mole

bp: 156°C (at 760 mm Hg)

vp: 4.3 mm Hg (at 25°C)

Bromobenzene metabolism has been under investigation since the 1930's at which time it was reported that both dogs and mice metabolize bromobenzene to a mercapturic acid, specifically p-bromophenylmercapturic acid (1). Recent studies on the metabolism of bromobenzene have both confirmed the existence of metabolites reported in earlier studies and determined the presence of previously unknown metabolic products. Several researchers have identified an intermediate metabolite, bromobenzene-3,4-epoxide, which is formed by a cytochrome P-450 enzyme system within the endoplasmic reticulum of the liver (2, 3, 4, 5). This intermediate is broken down to a variety of compounds including: 3,4- and 2,3-bromocatechol (2, 11), 2-, 3-, and 4- bromophenol (2, 3, 5, 6, 11, 12) and 2,3- and 3,4-bromophenyldihydrodiol (2, 5, 11). Additionally it has been reported that up to six percent of bromobenzene is eliminated unchanged in expired breath or feces (6, 7).

The majority of the bromobenzene metabolites are excreted in the urine in conjugated form (2, 5, 6, 8). Spencer and Williams (8) administered bromobenzene to rabbits orally, and upon subsequent urine analyses noted the presence of the conjugates mercapturic acids, glucuronides and ethereal sulfates, in approximately a 2:3:3 ratio (accounting for 97.9% of the dosage). They suggested that oxygen conjugation is greater than the sulfur conjugation. This theory was supported by Williams (6) who found that 58% of a bromobenzene dosage was excreted as o-conjugates.

Based on the results of studies in which male rats were given ^{14}C-bromobenzene i.p., Jollow et al. (2), suggested a detailed pathway for the metabolism of bromobenzene (Figure 1). According to the proposed metabolic process, bromobenzene is initially broken down to the intermediate bromobenzene-3,4-epoxide.

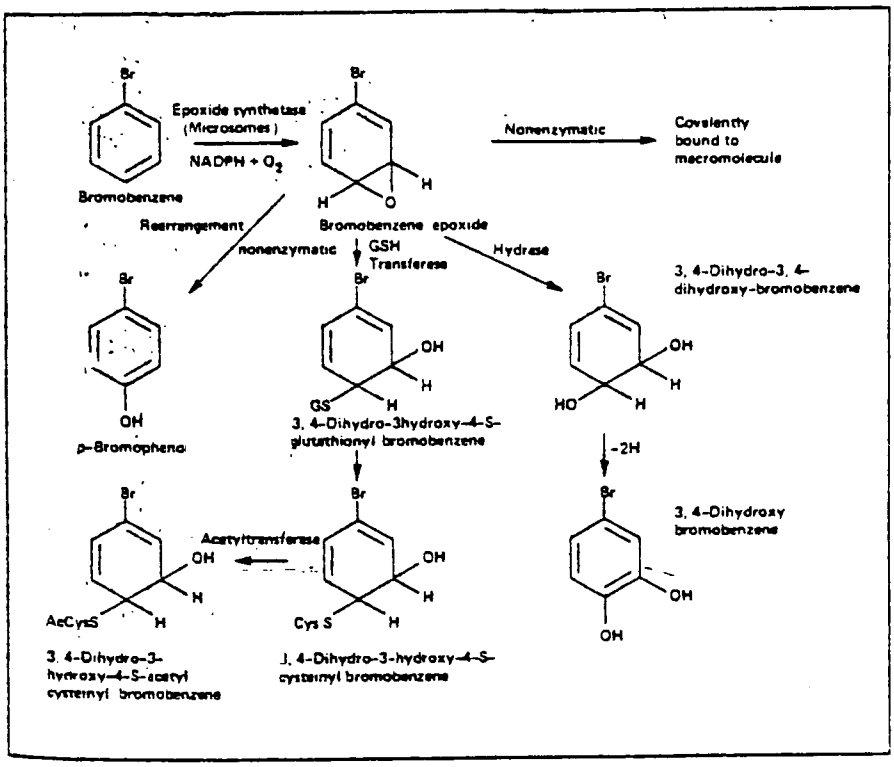


Fig. 1 (2).
Pathway of metabolism of bromobenzene in rats.

The epoxide intermediate is converted to 3,4-dihydro-3,4'-dihydroxy-bromobenzene by an epoxide hydratase enzyme (5). This compound is in turn dehydrogenated to 4-bromocatechol (2). Azouz et al. (9), found 28% of a bromobenzene dosage administered to rabbits was excreted in urine as 4-bromocatechol (mostly in conjugated form), with peak excretion occurring for the first two days.

Nonenzymatic rearangement of the epoxide intermediate leads to the formation of p-bromophenol (2). Azouz (9) found small amounts of p-bromophenol (2-3% of dosage) in the urine of rabbits following bromobenzene administration. Ruzo et al. (3), reported the presence of 3- and 4-bromophenol as metabolites of bromobenzene in rabbits. Bromophenol is also formed by the alkylation of glutathione (GSH) by the epoxide intermediate metabolite within the biliary system (2, 4). Sipes et al. (4), using rats, determined that within 3 hours post administration 56% of dosed bromobenzene was present in the bile. They suggested that the bromophenol excreted in the bile is reabsorbed from the intestine and eventually excreted in the urine.

Bromophenylmercapturic acid was determined to be present in the urine of rats following bromobenzene intoxication (4). Azouz et al. (9), found the compound accounted for 22% of a bromobenzene dosage excreted in the urine of rabbits. Gillham and Young (10) however suggest that the mercapturic acid conjugate is a product of the addition of HCl during urine analysis. Using rats subcutaneously injected with bromobenzene, they were

able to isolate an acid-labile precurser of p-bromophenylmercapturic acid. The authors found N-acetyl-S-(4-bromo-1,2-dihydro-2-hydroxyphenyl)-L-cysteine to be a premercapturic acid formed in bromobenzene metabolism. This compound was reduced to p-bromophenylmercapturic acid and p-bromophenol upon addition of HCl (10).

The distribution of bromobenzene metabolites in rats following administration of the chemical in a single toxic dose was determined by Zamoaglione et al. (12). They found the metabolites bromophenylmercapturic acid, 4-bromophenol, bromocatechol, bromophenyl dihydrodiol and 2-bromophenol comprising 48±5, 37±4, 6±2, 4±1 and 4±1% of the total urinary metabolites respectively. In a similar experiment, rats were administered bromobenzene in a non-toxic dose, and the same metabolites were found but in different ratios. The metabolites were present as 70±5, 18±4, 4±2, 4±1, and 3±1% of the total, respectively (12). Jollow et al. (2), in studies with rats, attributed the variation in bromophenylmercapturic acid content to the amount of glutathione present in the liver and available for conjugation with the expoxide intermediate. In the case of a toxic dose (10 mmol/kg), the glutathione became the rate-limiting factor for mercapturic acid formation (2).

Studies to determine the mechanism of renal necrosis induced by bromobenzene intoxication were conducted by Reid et al. (13), and Reid (14). Rats were administered bromobenzene intraperitoneally and 24 hours later tissue levels were determined by GLC (Table 1) (13). Adipose tissues were found to concentrate bromobenzene to a greater extent than the blood plasma. The authors suggested the metabolic intermediate bromobenzene-3, 4-epoxide to be the cause of tissue damage following bromobenzene exposure (13, 14).

Table 1 (13).

Tissue distribution of bromobenzene. Four or 24 h after administration of bromobenzene (750 mg/kg i.p.) tissue levels were determined by GLC in all organs except fat where the level was calculated from the specific activity of ^{3}H-bromobenzene (1 mCi/mmol)

Tissue	Bromobenzene Concentration 4 h ug/g ± SE	24 h ug/g ± SE
Plasma	34 ± 5	2.1 ± 0.4
Liver	282 ± 32	10.7 ± 1.2
Kidney	235 ± 50	18.9 ± 4.6
Brain	206 ± 27	7.0 ± 1.4
Heart	146 ± 21	5.0 ± 1.2
Lung	142 ± 41	6.2 ± 1.0
Stomach	132 ± 37	16.8 ± 6.1
Fat	5,600 ± 900	400 ± 150

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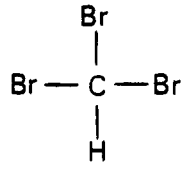
BROMOFORM

$CHBr_3$



CAS: 000075252

Syn: tribromomethane; methenyl tribromide

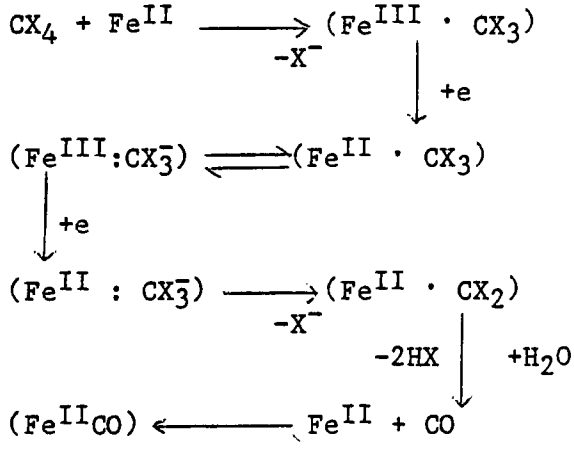
Mol wt: 252.75 g/mole

bp: 149.5°C (at 760 mm Hg)

vp: 6.11 mm Hg (at 25°C)

On the basis of in vitro studies using hepatic microsomal fractions from Long-Evans rats, Ahmed et al., suggested that bromoform is metabolized to CO by a microsomal cytochrome P-450-dependent mixed-function oxidase system (1).

Wolf et al.(2), also studied the in vitro metabolism of bromoform using rat hepatic microsomal fractions. The following general reaction sequence, involving reductive metabolism to a carbene ligand, was proposed to explain the formation of CO (2):



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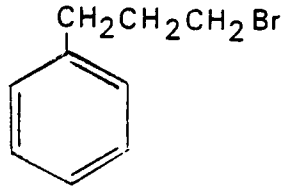
3-BROMOPROPYLBENZENE

$C_9H_{11}Br$



CAS: 637-59-2

Syn: 1-bromo-3-phenylpropane

Mol. wt.: 199.10 g/mole

bp: 110°C (at 12 mm Hg)

The metabolism of 3-bromopropylbenzene in rabbits was reported by Bray et al. (1). Rabbits were administered the compound by stomach tube as a suspension in water in doses of 0.25g 3-bromopropylbenzene per kg. Urinary metabolites were determined quantitatively by ether extraction, fractional crystallization, and paper chromatography.

About 89% of the administered dose was accounted for in urine, of which 20% was ethereal sulphate and 69% was ether soluble acid. The ether soluble acids included the major metabolite glucosiduronic acid and smaller amounts of mercapturic acid and glycine conjugates. The authors suggested that the excretion of large amounts of glucosiduronic acid and ethereal sulphate indicate the formation of phenolic intermediates, (3-bromopropyl)-phenol probably being the major intermediate (1).

In addition, two metabolites were identified in the unhydrolysed urine (acidic) fraction: phenaceturic acid and N-acetyl-S-(3-phenylpropyl)-L-cysteine. Also, phenolic metabolites were detected but not identified in the hydrolysed urine (conjugated phenolic) fraction (1).

REFERENCE

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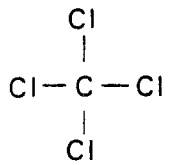
CARBON TETRACHLORIDE

CCl_4



CAS: 000056235

Syn: methane tetrachloride; tetrachloromethane; perchloromethane

Mol wt: 153.82 g/mole

bp: 76.54°C (at 760 mm Hg)

vp: 98.9 mm Hg (at 25°C)

The metabolism of carbon tetrachloride has been studied extensively in various animal species and two major metabolites have been determined: chloroform ($CHCl_3$) and carbon dioxide (CO_2). Lesser concentrations of hexachloroethane (C_2Cl_6) have also been identified, and large portions of the CCl_4 are reportedly expired unchanged in the breath.

Two major theories for CCl_4 detoxification are presented in the literature. In both theories the metabolism begins with dehalogenation of the compound within the liver and, to a lesser extent, the kidney (1,2,3). One theory attributes the dehalogenation to a non-enzymatic reaction involving sulfhydryl compounds (1,2). As explained by Bini et al. (2), CCl_3 radicals derived from the CCl_4 extract a hydrogen atom from sulphydric groups thereby forming $CHCl_3$, or they recombine by dimerization to yield C_2Cl_6. The second theory suggests that the conversion of CCl_4 to its metabolites is initiated by an hepatic enzyme system (3,4). Paul and Rubinstein (3) found that no significant dehalogenation occured in vitro when liver slices were exposed to the sulfhydryl compounds glutathione and cysteine, thereby lending support to the latter theory.

The largest portion of a CCl_4 dose is expired unchanged in the breath regardless of administrative route. Humans administered 80 ppm CCl_4 in a single breath, expired 33% of the dosage unchanged within one hour (5). Monkeys exposed to the compound in air (50 ppm for 139 to 300 minutes) expired 40% unchanged within 1800 hours (6); and, after 18 hours rats had expired 75% of an intra-duodenally administered CCl_4 dose (1 ml/kg) (3).

A transitory accumulation of CCl_4 in the body tissues was reported by Fowler (7). Six hours after the administration of 1 ml CCl_4/kg to rabbits, 787 ug/g was accumulated in the adipose tissue. Forty-eight hours post-dosing the CCl_4 level had decreased to 45 ug/g. In related studies with sheep (0.12 or 0.15 ml/kg, intra-ruminal), Fowler (8) found CCl_4 present in the bile; the maximum biliary concentration of CCl_4 (4-5 ug/ml) occurred 1-3 hours after dosing and fell below one ug/ml within six hours. Traces of CCl_4 were noted in sheeps' urine for up to seven days following a 0.1 or 0.12 mL/kg intraruminal dose (8). CCl_4 was also evident in the blood of rabbits immediately following a 4-hour exposure to the compound in air (9).

The majority of $CHCl_3$ formed during the metabolism of CCl_4 is found in the liver and kidney. Bini, et al. (2), administered 0.1-0.5 mL CCl_4 directly to the stomach of rats (200 g) and 15 minutes later found 0.037 mg $CHCl_3$/g in the liver. The metabolite level decreased to 0.007 mg/g within four hours. Similarly, in rabbits (1.5 to 3.0 kg) the maximum $CHCl_3$ concentration, following a 1.0 ml CCl_4/kg dosage administered by stomach tube, occurred in the liver six hours after administration of the compound (7). Significant amounts of $CHCl_3$ have also been found in the bile and urine of test animals (8).

The presence of $CHCl_3$ in the expired air of animals exposed to CCl_4 has also been reported (1,3,10); yet when compared to unchanged CCl_4 expiration the quantity is minimal (ratios reported in dogs were between 1:1000 and 1:4000(1)).

The conversion of CCl_4 to CO_2 accounts for less than 5% of administered CCl_4 (3). Paul and Rubinstein (3) found that CO_2 is a product of both CCl_4 and $CHCl_3$ metabolism, the $CHCl_3$ to CO_2 reaction proceeding more rapidly. These findings lead to the possibility that $CHCl_3$ may act as an intermediate in CCl_4 metabolism and account for the most of CO_2 produced (3).

Hexachloroethane was determined to be a minor metabolite of CCl_4 (2,4,7,8,11). The maximum concentration of C_2Cl_6 (16.5 ng/g) following a 1.0 mL/kg oral dose in rabbits was found in the adipose tissue, 24 hours after exposure (7). Bini, et al. (2), found a C_2Cl_6 concentration of 0.005 mg/g in organ homogenate 4 hours after a 0.1 to 0.5 ml dosage of CCl_4 was administered to rats (200 g) via stomach tube.

Tissue concentrations of CCl_4, $CHCl_3$ and C_2Cl_6 following administration by stomach tube of 1.0 ml CCl_4/kg to rabbits were determined by Fowler (7). The results, as seen in Table 1, indicate that CCl_4 and C_2Cl_6 accumulate mainly in the fat while $CHCl_3$ is found to a great extent in both the liver and fat tissues.

Table I (7)

Concentrations of carbon tetrachloride (CCl_4, µg/g ± S.D.), chloroform ($CHCl_3$, µg/g ± S.D.) and hexachloroethane ($CCl_3.CCl_3$, ng/g ± S.D.) in rabbit tissues following administration of carbon tetrachloride (1 ml./kg)

Tissue and sample time		No. of rabbits	CCl_4	$CHCl_3$	$CCl_3.CCl_3$
6 hr	Fat	5	787 ± 289	4·7 ± 0·5	4·1 ± 1·2
	Liver	5	96 ± 11	4·9 ± 1·5	1·6 ± 0·5
	Kidney	5	20 ± 13	1·4 ± 0·6	0·7 ± 0·2
	Muscle	5	21 ± 12	0·1 ± 0·1	0·3 ± 0·2
24 hr	Fat	5	96 ± 11	1·0 ± 0·2	16·5 ± 1·6
	Liver	5	7·7 ± 1·3	1·0 ± 0·4	4·2 ± 1·8
	Kidney	5	6·9 ± 3·9	0·4 ± 0·2	2·2 ± 1·1
	Muscle	5	1·3 ± 0·6	0·1 ± 0·1	0·5 ± 0·2
44 hr	(Died)				
	Fat	1	23	1·4	10·0
	Liver	1	1·1	4·4	3·1
	Kidney	1	0·5	0·4	2·2
	Muscle	1	0·3	Trace	9·2
48 hr	Fat	4	45 ± 12	0·4 ± 0·1	6·8 ± 2·4
	Liver	4	3·8 ± 0·1	0·8 ± 0·2	1·0 ± 0·3
	Kidney	4	0·5 ± 0·3	0·2 ± 0·0	Trace
	Muscle	4	0·5 ± 0·3	0·1 ± 0·1	Trace

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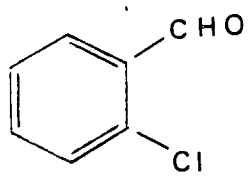
CHLOROBENZALDEHYDE

C_7H_5ClO



CAS: 000089985

Syn: 2-chlorobenzaldehyde; ortho-chlorobenzaldehyde

Mol. Wt.: 140.57 g/mole

bp: 211.9°C (at 760 mm Hg); 84.3°C (at 10 mm Hg)

vp: 1.07 mm Hg (at 32.1°C)

In a 1973 study using both rats and cats, Leadbeater (1) found that o-chlorobenzaldehyde is readily absorbed from both the gastrointestinal and respiratory tracts. In vitro tests using blood samples from rats, cats and humans gave half-lives for o-chlorobenzaldehyde (initial concentrations of 2.65 uM) of 15, 70 and 15 seconds, respectively (1).

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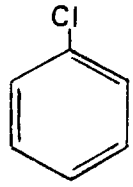
CHLOROBENZENE

C_6H_5Cl



CAS: 000108907

Syn: benzene chloride; chlorbenzene; MCB; monochlorbenzene; monochlorobenzene; phenyl chloride

Mol wt: 112.56 g/mole

bp: 132°C (at 760 mm Hg)

vp: 11.8 mm Hg (at 25°C)

In 1950, Spencer and Williams (1) studied the metabolism of chlorobenzene in the rabbit. Three chinchilla rabbits, kept on a controlled diet and allowed water ad libitum, were each administered 150 mg chlorobenzene/kg via stomach tube. Upon analysis of daily urines, it was found that mercapturic acids, glucuronides and ethereal sulfates were excreted in roughly equal amounts (20.4, 25.2, and 26.6% of the dosage, respectively) for a total of 72.2% of the administered dosage. Ethereal sulfate and glucuronide levels were above normal for only one day. Excretion of mercapturic acid, however, was measurable for two days post-dosing.

In a follow-up study in which rabbits were administered 10 or 12 g of chlorobenzene by stomach tube, Smith, et al. (2), reported results similar to those of Spencer and Williams (1). The major metabolites found were the ethereal sulphate and glucuronide conjugates of 4-catechol, and p-chlorophenylmercapturic acid. Minor metabolites were reported as p-chlorophenol and its glucuronide (about 0.5% of the dose, combined) and 3,4-dihydro-3,4-dihydroxychlorobenzene (about 0.03%).

These results were later verified by Azouz et al. (3), Williams (4), and Parke and Williams (5). Azouz et al. (3), found that, following oral administration of 0.5 g/kg of chlorobenzene to rabbits, 37% of the given dose was excreted in urine as catechol derivatives and 28% was eliminated as mercapturic acids. Chlorobenzene also formed small amounts (2-3%) of p-chlorophenol and traces of o-chlorophenol. Williams (4) reported urinary excretion of catechols and mercapturic acids in amounts of 27% and 25%, respectively, from studies in which rabbits had received 0.5 g/kg chlorobenzene orally. In addition, Azouz et al. (3), and Williams (4) reported

that rabbits expired 27% of the oral dose (0.5 g/kg) as unchanged chlorobenzene.

Several explanations for metabolite formations were described in the literature. Smith et al. (2), suggested an intermediate perhydroxylation process resulting in the formation of 3,4-dihydro-3,4-dihydroxy chlorobenzene which then undergoes either dehydrogenation to form 4-chlorocatechol or dehydration to form p-chlorophenol. The authors (2) concluded that chlorobenzene undergoes oxidation more extensively than it undergoes cysteine conjugation, and that most of the oxidized chlorobenzene appears as 4-chlorocatechol.

Gillham and Young (6), were able to isolate an acid-labile precursor of p-chlorophenylmercapturic acid from the urine of rats injected with chlorobenzene. They concluded that N-acetyl-S-(4-chloro-1, 2-dihydro-2-hydroxyphenyl)-L-cysteine was the premercapturic acid formed in chlorobenzene metabolism and that this compound was broken down to p-chlorophenylmercapturic acid and chlorophenol upon the addition of HCl during urine analysis.

Smith et al. (7), in 1972, conducted an in-depth study of chlorobenzene metabolism using ^{14}C-tagged chlorobenzene. Two female Dutch rabbits were administered 0.5 g of radioactive chlorobenzene (75.0 uci) twice daily for four days. Urine and fecal samples were collected separately for a 7-day period, beginning with the first dosing day. The excreta were then analyzed for metabolites, and one animal was sacrificed for tissue accumulation studies.

Of the dosage, 19.6% was recovered in the urine, 2.6% in the feces and only .005% was retained in the body tissues. In agreement with previous studies (3,4), the authors concluded that a large percentage of the tagged chlorobenzene was lost through respiration. Table 1 shows the major classes of chemicals found in the urine along with metabolite distribution (7).

As reported in earlier studies, the major metabolites of chlorobenzene were the conjugates: ethereal sulfates, mercapturic acids and glucuronides. Less than eight percent of the metabolites consisted of free state phenols and 3,4-dihydro-3,4- dihydroxy-chlorobenzene (7)

Table 1 (7)

Distribution of radioactive metabolites in the urine of rabbits dosed with [^{14}C]chlorobenzene

Metabolite	Radioactivity (10^{-6} d.p.m.)	% of total urinary radioactivity
3,4-Dihydro-3,4-dihydroxychlorobenzene	0·182	0·57
Monophenols	0·898	2·84
Diphenols	1·320	4·17
Mercapturic acids	7·530	23·80
Ethereal sulphates	10·720	33·88
Glucuronides	10·620	33·57
Total	31·270	98·83

The authors suggested that 3,4-chlorobenzene oxide is the only initial metabolite resulting from chlorobenzene exposure. Hydration and dehydrogenation reactions with the oxide lead to the formation of 4-chlorocatechol, the major diphenolic metabolite, and less frequently to 3-chlorocatechol or chloroquinol. Catechol formation has also been attributed to the dehydrochlorination of 1,2-dihydro-1,2-dihydroxychlorobenzene (7).

Glutathione conjugation of the primary epoxide metabolite leads to the formation of the premercapturic acid, N-acetyl-S-(4-chloro-1,2-dihydro-2-hydroxy-phenyl)-L-cysteine. According to Gillham and Young (6), this acid-labile compound is decomposed by the addition of acid, during analysis, to yield p-chlorophenylmercapturic acid and monochlorophenols. Smith et al. (7) proposed a mechamism by which all three isomers (o-, m-, and p-) of chlorophenolmercapturic acid may be formed.

Other sources of o-, m-, and p-chlorophenol formation are believed to exist (7). Several theories are presented by researchers; however, no single formation process has been determined.

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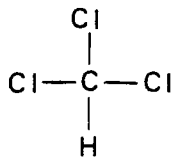
CHLOROFORM

$CHCL_3$



CAS: 000067663

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

Mol wt: 119.38 g/mole

bp: 61.7°C (at 760 mm Hg)

vp: 173.1 mm Hg (at 25°C)

The metabolic fate of chloroform ($CHCl_3$) has been extensively studied, in part due to the past use of the compound as an anaesthetic. It has been reported by several researchers that the major mode of excretion of the compound and its primary metabolite, carbon dioxide (CO_2), occurs through expired air (1-8). Additional tolulene-soluble metabolites (specific makeup not determined) have been noted in expired air as well as the presence of carbonate and bicarbonate species in the urine (1,2). Recent studies (10, 11, 12) have revealed the presence of an intermediate metabolite, phosgene (formed by microsomal oxidation of the parent compound), which may be responsible for a portion of the CO_2 formed during chloroform metabolism.

The excretion of unchanged chloroform in expired breath has been found to vary in different test animal species. Expiration levels of the unchanged compound in mice, rats, and monkeys was determined by Brown et al. (2) using ^{14}C-chloroform administered orally. After 48 hours 6% of the dose was present unchanged in the expired air of mice, 20% in rats, and 79% in the squirrel monkey. Similar excretion results were reported by Charlesworth (1) and Paul and Rubinstein (4). Fry et al. (3), administered 500 mg ^{13}C-chloroform tablets to adult men and women and found up to 68.3% of the dosage was expired unchanged. Within the first eight hours after chloroform dosing, between 17.8 and 66.6% of the dosage was expired and by 24 hours post-dosing expired concentrations were below measurable quantities. One hour after a single-breath dose of chloroform, Morgan et al. (9), determined that human volunteers expired 10% of the dosage unchanged via the lungs.

Analysis of chloroform levels in blood showed a linear relationship between blood chloroform levels and pulmonary excretion of the compound (3).

Varying pulmonary excretion rates of chloroform were found to exist between the males and females of test species. The males of each species tended to retain more of the administered dosage than did the females (1). Additionally, Fry et al. (3), found higher retention rates in obese subjects than in those of normal weight. These findings led to the conclusion that the adipose tissue may act as a sink for chloroform (3).

The pulmonary expiration of the primary metabolite CO_2, like the excretion of chloroform, varies according to the species studied. Eighty percent of a chloroform dose administered to mice was expired in the breath after 48 hours; 66% in rats, and 16% in monkeys (2). Fry et al. (3), determined up to 50.6% of a ^{13}C-chloroform dose was expired as CO_2 in humans. Maximum CO_2 concentrations were expired between 75 and 210 minutes following administration (3).

Researchers have concluded that the pulmonary excretion of unchanged chloroform and the primary metabolite CO_2 account for the vast majority of an administered $CHCl_3$ dose (2,3). Lesser metabolites have been found by researchers working with various animal species; however, their presence is minimal in comparison to the excretion of $CHCl_3$ and CO_2. Charlesworth (1) administered ^{14}C-chloroform to mice in a dosage of 60 mg/kg and found 13% of the radioactivity present as bicarbonate and carbonate in the urine. Similar results were reported by Brown et al. (2), who found bicarbonate and/ or carbonate and ^{14}C-urea in the urine of rats and mice.

The biotransformation of chloroform to carbon dioxide could follow the following reaction presented by Fry et al. (3):

$$CHCl_3 + H_2O + O \longrightarrow CO_2 + 3HCl$$

The accumulation of chloroform in the adipose tissue of exposed species leads to extensive biotransformation of the compound to CO_2 at that site (3).

Recently it has been determined that phosgene ($COCl_2$) is a reactive intermediate metabolite of chloroform, acting as a precursor to carbon dioxide formation. The metabolite is formed during the microsomal oxidation of chloroform in the liver (10,11). Due to its electrophilic nature, phosgene reacts in the liver with nucleophiles, undergoing hydrolysis to form CO_2, or reacting with nucleophilic groups to form irreversible covalent bonds. Schematic representations of phosgene formation and subsequent reactions are shown in Figure 1 (10).

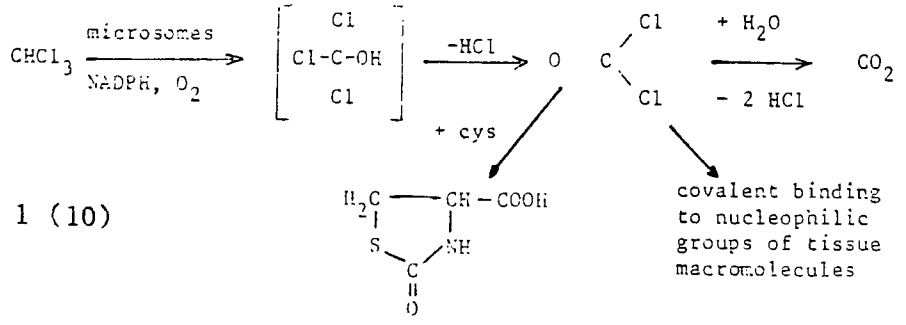


Figure 1 (10)

4-carboxy-thiazolidine-2-one.

Proposed metabolism of chloroform.

It has been suggested by some researchers that the toxic effect of chloroform is caused by the irreversible binding of phosgene to protein molecules within the liver and kidney (10,12).

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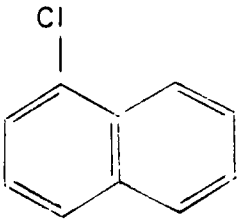
CHLORONAPHTHALENE

$C_{10}H_7Cl$

Mol wt: 162.62g/mole



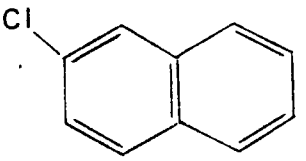
1-chloronaphthalene

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-chloronaphthalene

CAS: 000091587

Syn: beta-chloronaphthalene

bp: 256°C (at 760 mm Hg); 106.5°C (at 5 mm Hg)

Following administration of 1-chloronaphthalene (1 g, by stomach tube) to male albino rabbits, Cornish and Block, 1958 (1), were able to account for 79% of the administered compound as urinary metabolites within 4 days. Of the administered dose, 54% was excreted as glucosiduronic acid, 13% as mercapturic acid, 10% as ethereal sulfate and 2% as free phenolic compounds.

In a 1975 study, Ruzo et al. (2), identified the hydroxylated metabolites of 1- and 2-chloronaphthalene following retrocarotid injection of the compounds (30 mg/kg) into 10-kg pigs. Analysis of urine collected 5 hours after dosing showed 4-chloro-1-naphthol to be the major phenolic metabolite of 1-chloronaphthalene, and 3-chloro-2-naphthol to be the major phenolic metabolite of 2-chloronaphthalene.

In a 1976 study, Ruzo et al. (3), found that following retrocarotid injection (300 mg in 7.5-kg pigs), 1- and 2-chloronaphthalenes were distributed in various organs (brain, kidney, liver, lung, skeletal muscle, psoas, heart and fat). Metabolism of the chloronaphthalenes in pigs was found to be rapid, being virtually complete within 4 hours. Metabolites of the chloronaphthalenes were found to be localized in the kidney, liver, urine and bile.

On the basis of their studies with pigs, Ruzo et al. (4), suggested that the metabolism of 1-chloronaphthalene involves the formation of an arene oxide intermediate. Decomposition of the intermediate to form 4-chloro-1-naphthol is accompanied by a 1,2-H shift.

Studies by Sundstrom and coworkers (5,6), on the metabolism of chloronaphthalenes in frogs, report findings consistent with those reported above.

References

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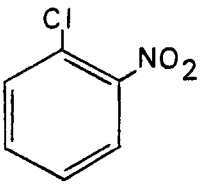
CHLORONITROBENZENE
$C_6H_4ClNO_2$
Mol wt: 157.56 g/mole

ortho-chloronitrobenzene

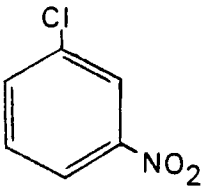


CAS: 000088733

Syn: chloro-o-nitrobenzene;
o-chloronitrobenzene;
1-chloro-2-nitrobenzene;
2-chloro-1-nitrobenzene;
o-nitrochlorobenzene; ONCB

bp: 246°C (at 760 mm Hg)

meta-chloronitrobenzene

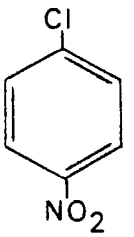


CAS: 000121733

Syn: chloro-m-nitrobenzene;
m-chloronitrobenzene;
1-chloro-3-nitrobenzene;
m-nitrochlorobenzene

bp: 235-6°C (at 760 mm Hg)

para-chloronitrobenzene



CAS: 000100005

Syn: p-chloronitrobenzene;
1-chloro-4-nitrobenzene;
4-chloro-1-nitrobenzene; p-chloronitrobenzene

bp: 242°C (at 760 mm Hg)

Bray et al. (1), reported the metabolism of chloronitrobenzene isomers and chloroaniline (ortho, meta, para) in the rabbit. Female rabbits (2-3 kg) were given either 0.1g of o-chloroni- trobenzene, or 0.2 g of m- or p-chloronitrobenzene, per kg body weight. The method of administration was not stated. Feces were collected for 2 days and urine was collected daily, usually for 2 days, until metabolites were no longer excreted. The samples were qualitatively and quantitatively analyzed by ether extraction and paper chromatography.

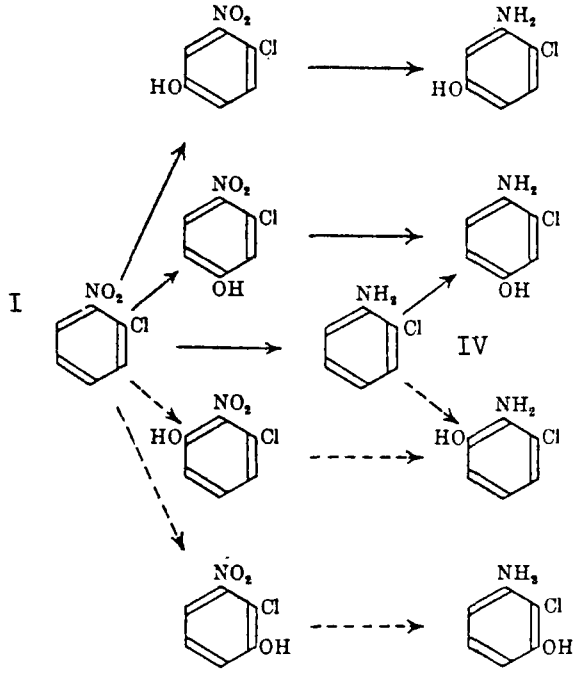
The majority of each chloronitrobenzene compound was excreted as ether glucuronides (19-42% of the administered dose) and ethereal sulphates (18-24%), which represented acid-conjugated compounds of aminochlorophenols and chloronitrophenols. Free chloroaniline was a metabolite of all 3 chloronitrobenzene isomers and accounted for 9-11% of the dose; the p-isomer also produced a small amount (4%) of conjugated chloroaniline. Some nitrophenylmercapturic acid (about 7%) was formed from the o- and p-chloronitrobenzenes. The unabsorbed material (0.3-2.8%) found in feces was completely reduced to chloroaniline with the exception of samples from rabbits given the p-chloronitrobenzene isomer, in which case some unchanged p-chloronitrobenzene was found in addition to chloroaniline. For all 3 isomers of chloronitrobenzene, trace amounts of free phenolic metabolites were detected. No evidence of unchanged chloronitrobenzene was found in the urine samples. The urinary metabolites were further identified by paper chromatography as shown in Table 1 (1).

The main metabolic processes responsible for chloronitrobenzene degradation in the rabbit were reduction and hydroxylation. Figure 1 represents the metabolism of chloronitrobenzene and chloroaniline isomers (1).

Evidence supporting the formation of chloroaniline from o- and p-chloronitrobenzene was reported by Renshaw & Ashcroft (2). An incidence of toxic symptoms in chemical plant workers due to inhalation of chloronitrobenzene vapors led to suggestion that the compound may be reduced by hemoglobin to amidochlorobenzene (chloroaniline). Reduction may occur in the lungs, body tissues, or liver cells.

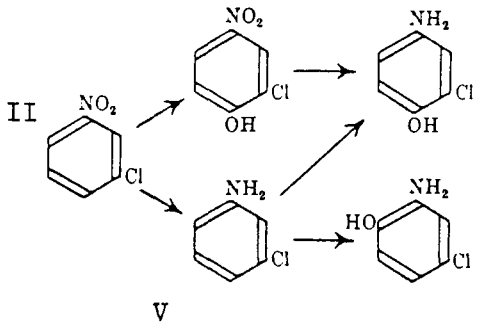
Table 1 (1). Urinary metabolites of rabbits exposed to 0.1 g/kg o-chloronitrobenzene or 0.2 g/kg m- or p-chloronitrobenzene. Metabolites were identified by paper chromatographic analysis of 4 types of urine extracts. Compounds in parenetheses were present in trace amounts.

ortho-chloronitrobenzene	meta-chloronitrobenzene	para-chloronitrobenzene
N-acetyl-S-(2-nitrophenyl)-L-cysteine	2-amino-4-chlorophenol	N-acetyl(-S-(4-nitrophenol)-L-cysteine
2-amino-3-chlorophenol	4-amino-2-chlorophenol	2-amino-5-chlorophenol
(3-amino-2-chlorophenol)	m-chloroaniline	p-chloroaniline
3-amino-4-chlorophenol	2-chloro-4-nitrophenol	(2-chloro-5-nitrophenol)
4-amino-4-chlorophenol		
o-chloroaniline		
(2-chloro-3-nitrophenol)		
(3-chloro-2-nitrophenol)		
3-chloro-4-nitrophenol		
4-chloro-3-nitrophenol		



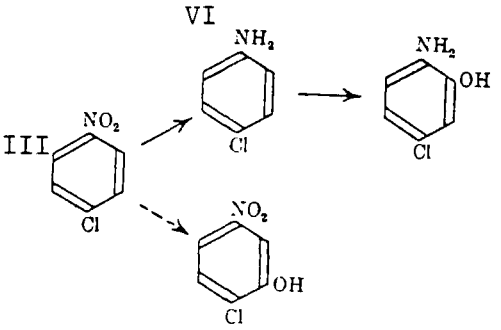
I) o-chloronitrobenzene

IV) o-chloroaniline



II) m-chloronitrobenzene

V) m-chloroaniline



III) p-chloronitrobenzene

VI) p-chloroaniline

Fig. 1 (1). Phenolic metabolites excreted (free or conjugated) in urine by the rabbit after dosage with o-, m- and p- chloronitrobenzene and o-, m- and p-chloroaniline. Broken arrows point to metabolites excreted only in very small amounts. (Although only a small amount of 4-chloro-3-nitrophenol was excreted following administration of o-chloronitrobenzene, it is likely that a much greater amount was formed and reduced to 3-amino-4-chlorophenol before it was excreted.)

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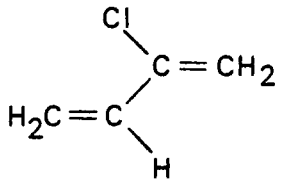
CHLOROPRENE

C_4H_5Cl



CAS: 000126998

Syn: chlorobutadiene; 2-chlorobuta-1,3-diene; 2-chloro-1,3-butadiene

Mol wt: 88.54 g/mole

bp: 59.4°C (at 760 mm Hg)

vp: 275 mm Hg (at 30°C)

Based on a review of the recent literature, Bardodej (1) suggests that chloroprene is metabolized by hepatic mixed-function oxidases, which catalyze the epoxidation of the compound. The author indicated that the carcinogenicity of chloroprene may be attributed to an epoxide of the compound.

Jaeger et al. (2), studied the effects of chloroprene on serum alanine-ketoglutarate transaminase (AKT) activity in rats. Adult male Holtzman rats (250-350 g) were used for inhalation experiments. After exposure to various concentrations (ranging from 500 ppm to approximately 10,000 ppm) of chloroprene in air, the rats were sacrificed and the blood was collected for determination of serum enzyme activity.

Results showed that AKT activity in rats varied with the time of day at which the rats were exposed to chloroprene (concentration was not specified for this experiment). This effect was related to the circardian rhythm of hepatic glutathione (GSH) concentrations observed in a previous experiment with non-exposed rats. In addition, fasted rats had overall lower GSH levels than normal-diet fed rats. It was concluded that when rats were exposed to chloroprene at times of lowered GSH concentration, the level of serum AKT activity increased and the toxic effect of chloroprene was potentiated.

A dose-response relationship for serum AKT activity was also observed. Furthermore, rats which were fasted prior to chloroprene exposure showed increased levels of AKT activity at all concentrations tested; rats which were fed before exposure were not affected at chloroprene levels of 500, 1,000 and 2,000 ppm. The authors concluded that fasted rats were more susceptible than fed rats to the toxic effects of chloroprene.

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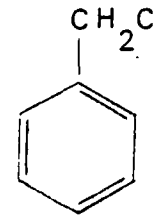
CHLOROTOLUENE
C_7H_7Cl
Mol wt: 126.59g/mole



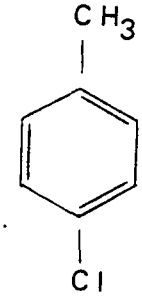
alpha - chlorotoluene

CAS: 000100447

Syn: benzyl chloride; chloromethyl benzene; tolyl chloride; chlorophenyl methane

bp: 179.3°C (at 760 mm Hg); 66°C (at 11 mm Hg)

vp: 1.3 mm Hg (at 25°C)



p - chlorotoluene

CAS: 000106434

Syn: p-tolyl chloride; 4-chloro-1-methyl benzene

bp: 162°C (at 760 mm Hg); 44°C (at 10 mm Hg)

vp: 3.5 mm Hg (at 25°C)

On the basis of a series of tests using rats, Knight and Young (1) concluded that, unlike many other simple halocarbon compounds, chlorotoluene is converted in vivo directly to a mercapturic acid metabolite, benzylmercapturic acid, without the intermediate formation of a premercapturic acid.

Bray et al. (2, 3, 4), after studying the metabolism of chlorotoluene in rats, rabbits and guinea pigs, proposed a 3-stage process for the formation of mercapturic acid:

1. the conjugation of the precursor with glutathione;

2. the hydrolysis of the glutathione conjugate by glutathionase to an S-substituted cysteine, glycine and glutamic acid;

3. the acetylatian of the S-substituted cysteine to mercapturic acid.

In addition to mercapturic acid metabolites, Bray et al. (2), also isolated benzoic and hippuric acid metabolites from the urine of rabbits treated with chlorotoluene. The authors suggested that these metabolites are formed via the intermediate formation of benzyl alcohols.

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3. Bray, H.G., T.S. Franklin, and S.P. James. 1959. The formation of mercapturic acids: 3. N-acetylation of S-substituted cysteines in the rabbit, rat and guinea pig. Biochem. Journ. 73:465-473.

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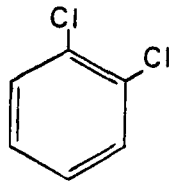
DICHLOROBENZENE

$C_6H_4Cl_2$

Mol wt: 147.01 g/mole

ortho-dichlorobenzene



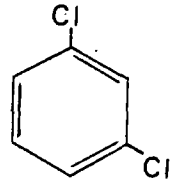
CAS: 000095501

Syn: o-dichlorobenzene; 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



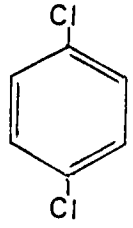
CAS: 541-73-1

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)

In a 1923 study of the fate of ortho- and meta-dichlorobenzene in dogs, Hele and Callaw (1) found that the administration of the compounds led to a corresponding rise of neutral sulfur in the urine. The authors suggested that such a rise indicates the presence of a mercapturic acid in the excreted urine; the specific constitution of the metabolite was not determined.

Azouz et al. (2,3,4), studied the metabolism of o- and p-dichlorobenzenes in chinchilla rabbits. The compounds were administered to the rabbits via stomach tube in doses of 0.5 g/kg. The ortho compound was suspended in water and the para isomer was administered as 25% (w/v)

solution in olive oil. Urine samples were collected daily and analyzed for metabolites using chromatographic methods. The major metabolite of o-dichlorobenzene was identified as 3,4-dichlorophenol, which represented about 30% of the dose administered. Minor metabolites were 2,3-dichlorophenol (9% of dose) and 3,4- and 4,5-dichlorocatechols (4% of dose). These compounds were excreted as o-conjugates with glucuronic and sulphuric acids. 3,4-Dichlorophenyl-mercapturic acid was also identified as a minor (5% of dose) metabolite. The metabolism of p-dichlorobenzene resulted in the excretion of conjugated 2,5-dichlorophenol (35% of dose) and 2,5-dichloroquinol (6% of dose). No catechol or mercapturic acid was formed. The excretion of o-dichlorobenzene metabolites peaked on the first day following administration and was completed by day 5 or 6. With p-dichlorobenzene, excretion of the metabolites peaked on the second day and was still appreciable on day 6 (4).

In a follow-up study, Parke and Williams (5) reported on the metabolism of the dichlorobenzene isomers, with special reference to the meta-isomer. Following oral administration of 0.5 g/kg of dichlorobenzene isomers to rabbits, six classes of compounds were determined to be metabolites of the dichlorobenzenes. These metabolites are listed in Table 1, along with their percentage of the administered dosage.

Upon further analysis of m-dichlorobenzene metabolism it was found that 20% of the dose was excreted as 2,4-dichlorophenol, while 3,5-dichlorophenol, 3,5-dichlorocatechol and 2,4-dichlorophenyl mercapturic acid were minor metabolites. Only half of the dose was accounted for. The excretion of the metabolites, as conjugates with glucuronic and sulphuric acids, reached a maximum on the first day after dosing and was complete within 5 days.

In an occupational study by Pagnotto and Walkley (6), a good correlation was found between the average air concentration of p-dichlorobenzene and the urinary excretion of dichlorophenol. Exposed workers showed rapid excretion of the metabolite, beginning shortly after exposure and peaking at the end of the work shift. Dichlorophenol excretion dropped off rapidly after terminiation of exposure, but was complete only after several days.

Table 1 (5).

Excretion of metabolites of dichlorobenzenes by rabbits

Dose fed was 0·5 g./kg. body wt. Results are expressed as percentage of fed dose.

Metabolite	Dichlorobenzene		
	ortho	*meta*	*para*
Glucuronide	48	36	36
Ethereal sulphate	21	7	27
Mercapturic acid	5	11	0
Total conjugates	74	51	63
Monophenols	39	25	35
Catechols	4	3	0
Quinols	0	0	*ca.* 6
Period of excretion	6† days	5† days	6‡ days

† Excretion of metabolites apparently complete.
‡ Excretion of metabolites not complete in 6 days.

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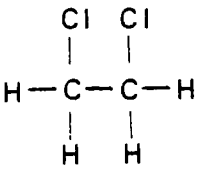
4. Azouz, W.M., D.V. Parke and R.T. Willliams. 1955. Studies in detoxication. 62. The metabolism of halogenobenzenes. ortho and para-Dichlorobenzenes. Biochem. J. 59: 410-415.

5. Parke, D.V. and R.T. Williams. 1955. Studies in detoxication. 63. The metabolism of halogenobenzenes. (a) meta-Dichlorobenzene. (b) Further observations on the metabolism of chlorobenzene. Biochem. J. 59: 415-422.

6. Pagnotto, L.D. and J.E. Walkley. 1965. Urinary dichlorophenol as an index of para-dichlorobenzene exposure. Am. Ind. Hyg. Assoc. J. 26: 137-142.

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/mole

bp: 83.47°C (at 760 mm Hg)

vp: 76.2 mm Hg (at 25°C)

In vivo studies on 1,2-dichloroethane metabolism in the mouse were reported by Yllner (1). Female albino mice were given an intraperitoneal injection of 0.05, 0.10, 0.14, or 0.17g of ^{14}C-labelled 1,2-dichloroethane per kg body wt., as a 10% solution in olive oil. Volatile metabolites, urine, and feces were collected every 24 hours for 3 days. Whole body homogenates were analyzed for remaining radioactivity at the end of the 3-day period. Radioactivity was measured by liquid scintillation and metabolites were identified by paper chromatography.

Analyses showed that the radioactivity was rapidly excreted, over 90% being eliminated in 24 hours at each dose level. The levels of activity in each constituent, depending on the dose, ranged as follows:

10-42% expired unchanged
12-15% expired as CO_2
51-73% detected in urine
0-0.6% found in feces contaminated with urine
0.6-1.3% remained in whole-body homogenate

The urinary metabolites excreted in 24-hours were further analyzed by isotope dilution techniques and the relative amount of each was expressed as a percentage of the total urinary radioactivity. Three major metabolites in urine were identified as chloroacetic acid (6-23%), S-carboxymethylcysteine (44-46% free and 0.05-5% conjugated), and thiodiacetic acid (33-34%). Small amounts of 2-chloroethanol (0.0-0.8%) and S,S'-ethylene-bis-cysteine (0.7-1.0%) were also detected. No oxalic acid was found. A minor portion of the radioactivity may be attributed to S-(Beta-hydroxyethyl)-cysteine and its mercapturic acid. The author proposed that 1,2-dichloroethane metabolism proceeds primarily via formation of chloroacetic acid. The metabolic processes may involve enzymatic dehalogenation of 1,2-dichloroethane and its intermediates (1).

In vitro experiments were also conducted in an effort to determine whether the metabolite S,S'-ethylene-bis-cysteine is formed by enzymatic reaction. 1,2-Dichloroethane and L-cysteine hydrochloride interacted in alkaline solution (pH 7.4) at 37°, resulting in the formation of the thioether S,S'-ethylene-bis-cysteine. No non-enzymatic reaction was observed. From the in vitro results it was suggested that S,S'-ethylene-bis-cysteine is probably formed enzymatically in vivo by the reaction of 1,2-dichloroethane and glutathione (1).

Similar data regarding the production of thioethers from the reaction of 1,2-dichloroethane with protein were reported by Morrison and Munro (2). In vitro experiments were conducted in which fish solids (freeze-dried cod filets) were refluxed with 10 volumes of 1,2-dichloroethane for 0.5 to 16 hours in order to determine the effects of the compound on the amino acids of fish protein. Analysis of the resulting acid hydrolysates and enzymatic hydrolysates indicated the destruction of cystine and histidine, and interference with the enzymatic release of methionine, histidine, and cystine. The authors suggested that the reactions involved alkylation by 1,2-dichloroethane of the sulfhydryl groups of protein, resulting in the production of thioether compounds such as S,S'-ethylene-bis-cysteine. To demonstrate the proposed alkylation process, S,S'-ethylene-bis-cysteine was synthesized by refluxing 10 g of L-cysteine (in 100 ml of 0.2M Na_2HPO_4) with 25 ml of 1,2-dichloroethane.

Nachtomi et al. (3), reported the urinary metabolites of 1,2-dichloroethane in the rat. Rats were treated by stomach tube with 100 mg of 1,2-dichloroethane in a soybean oil solution. Urine was collected for 24 hours and analyzed by paper chromatography and paper electrophoresis. The major metabolite was identified as S-(Beta-hydroxyethyl) mercapturic acid. Traces of S-(Beta-hydroxyethyl)cysteine were also detected.

Heppel et al. (4), suggested that 1,2-dichloroethane may be detoxified in rats by reaction with sulfur-containing compounds. Young male rats (33.3 - 46.1 g) were subjected to single or multiple 4-hour exposures to 1,000 ppm of 1,2-dichloroethane in air. Diets were supplemented with various sulfur-containing compounds including inorganic salts, amino acids, and organic S-compounds. Mortality and toxicity were recorded. It was

shown that the toxicity of 1,2-dichloroethane in rats was reduced by the following compounds: L-cystine and DL-methionine (amino acids), thiourea, thiouracil, 2-thiobarbituric acid, B,B'-dithiodiproprionic acid, L-cysteine hydrochloride, and thiolactic acid (only when administered i.p.). The authors noted that all the compounds listed can supply sulfhydryl groups for detoxifying 1,2-dichloroethane.

REFERENCES

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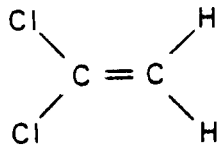
$C_2H_2Cl_2$



CAS:

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

Mol wt: 96.94

bp: 37°C(at 760 mm Hg)

vp: 633.7 mm Hg (at 25°C)

Prior to 1975, little information was available on the metabolism of 1,1-dichloroethylene (1,1-DCE; vinylidene chloride). Recently, however, it has been established that 1,1-DCE undergoes extensive, rapid metabolism. Most of an administered dose of 1,1-DCE is excreted unchanged through the lungs or as polar metabolites in urine. The metabolic products in urine include two major metabolites, thiodiglycollic acid and N-acetyl-S-cysteinyl-acetyl derivative, as well as chloroacetic acid, dithioglycollic acid, thioglycollic acid, and N-acetyl-S-(2-carboxymethyl)cysteine. The metabolic process involves oxidation of 1,1-DCE to the epoxide, structural rearrangement of the epoxide to form chloroacetic acid (a major intermediate), and subsequent conjugation of chloroacetic acid with glutathione to yield the final metabolites. 1,1-DCE is metabolized primarily in the liver and is glutathione-dependent.

Reichert and Werner (1) determined the metabolic fate of (^{14}C)1,1-DCE in rats after administration of a single oral dose of 0.5 or 50 mg per kg body weight. Analysis of radioactivity for 72 hours after administration showed that with the 0.5 mg/kg dose, about 0.9% was expired as unchanged 1,1-DCE, 23% was expired as $^{14}CO_2$, and 52% was eliminated in urine. At the 50 mg/kg level, the proportions of ^{14}C-activity were 20% unchanged 1,1-DCE, 6% $^{14}CO_2$, and 36% urinary radioactivity. Residual activity in the body after 72 hours amounted to 2-4% of the administered dose, and was located primarily in the liver, with minimal radioactivity present in other tissues. Similar data were reported by McKenna et al. (2), based on studies in which rats, fasted or fed, were given an oral dose of 1 or 50 mg of (^{14}C)1,1-DCE per kg body weight or were subjected to inhalation exposures

of 10 or 200 ppm of (^{14}C)1,1-DCE for 6 hours. Elimination of ^{14}C-activity was followed for 72 hours and the results, indicating the percentage of the dose that was metabolized, were reported as follows: with 10 ppm or 1 mg/kg, 97-99% was metabolized; with 50 mg/kg, 60-75%; and at 200 ppm, 92-96% was metabolized. The authors concluded that the fate of 1,1-DCE in the rat was dependent on both the dose and the route of administration.

The identities and proportions of 1,1-DCE metabolites in mice and rats were reported by Jones and Hathway (3). Metabolite determinations were made by scintillation, thin-layer and gas chromatography, and mass spectrometry for 3 days after oral administration of 50 mg of (^{14}C)1,1-DCE per kg body weight. The results are presented in Table 1. Mice metabolized over 20% more of the oral dose than did rats, which corresponded directly to the greater activity of cytochrome P-450 in mice.

A comprehensive metabolic scheme for 1,1-dichloroethylene in mammals was postulated by Jones and Hathway (3) as shown in Figure 1.

The first step in 1,1-DCE metabolism is the formation of the corresponding epoxide (3,4,5,6,7,8). 1,1-Dichloroethylene epoxide is highly unstable and short-lived, and has only recently been synthesized (5,6).

Table 1 (3).

Relative proportion of (^{14}C) excretory products after oral administration of 50 mg/kg of (1-^{14}C)DCE to rodents (observations 3 days after dosing)

(^{14}C) Excretory products	^{14}C expressed as % of dose	
	Mice*	Rats*
Unchanged DCE pulmonary	6	28
CO_2 excretion	3	3.5
Chloroacetic acid	0	1
Thiodiglycollic acid	3	22
Thioglycollic acid	5	3
Dithioglycollic acid	23	5
Thioglycollyloxalic acid	3	2
N-Acetyl-S-cysteinyl acetyl derivative	50	28
N-Acetyl-S-(2-carboxymethyl)cysteine	4	0
Urea	3	3.5

* Alderley Park strains.

The epoxide then undergoes rearrangement, primarily by the migration of one Cl atom and the loss of the other Cl atom, to yield chloroacetyl chloride (3,5,6,7) which is subsequently hydrolyzed to chloroacetic acid (7). A minor amount of chloroacetic acid may also be formed from 1,1-dichloroglycol, which is an intermediate derived from rearrangement of 1,1-DCE epoxide by hydrogen migration (7). The major and minor pathways of chloroacetic acid formation from 1,1-DCE are shown in Figure 2 (7).

One of the major urinary metabolites, the N-acetyl-S-cysteinyl acetyl derivative, is probably formed from the reaction of 1,1-DCE epoxide with glutathione, catalyzed by glutathione S-epoxide transferase (3,8).

The other main metabolite, thiodiglycollic acid, is formed from chloroacetic acid (3,8) through a series of degradative reactions, catalyzed by glutathione S-acyl transferase (8). Furthermore, thiodiglycollic acid was shown to undergo hydrolysis in vivo by the action of beta-thionase, producing the metabolites thioglycollic acid and dithioglycollic acid (3).

According to Hathway (8), the end products CO_2 and urea may be formed by the action of epoxide transferase on 1,1-DCE epoxide, or by the metabolism of chloroacetic acid.

Another possible metabolite of 1,1-DCE may be monochlorocitric acid, which Jaeger (9) suggests might be a conversion product of chloroacetic acid, based on the observation of increased hepatic citric acid concentrations in rats following inhalation exposure to 250 ppm of 1,1-DCE.

The extent of 1,1-DCE metabolism is glutathione-dependent, according to studies by McKenna et al. (2), in which fasted rats, with correspondingly lower hepatic glutathione levels, metabolized less (92%) of an inhaled dose of 1,1-DCE (200 ppm) than did fed rats (96% metabolized). Also, identification of the major urinary metabolites as thiodiglycollic acid and N-acetyl-S-cysteinyl acetyl derivative indicated the metabolism of 1,1-DCE via glutathione conjugation. Similarly, Jaeger et al. (10) concluded that glutathione was an important site of 1,1-DCE detoxification based on the results of earlier experiments (11) with rats, both in vivo and in isolated perfused rat liver. In general, therefore, researchers agree that 1,1-DCE is metabolized in the liver and is dependent on hepatic glutathione for detoxification.

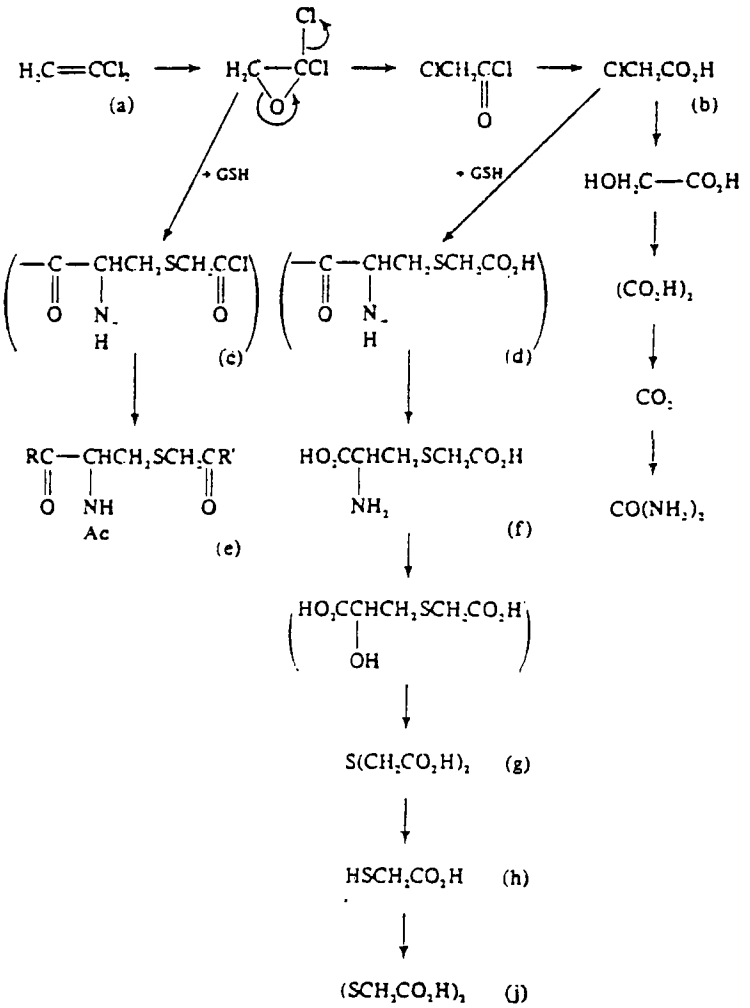
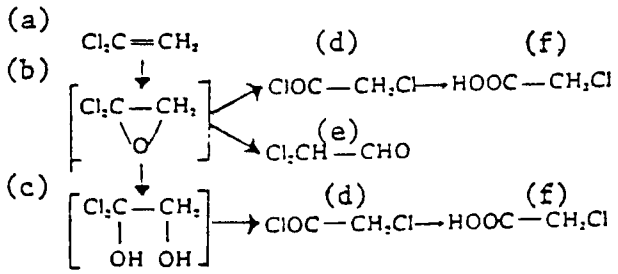


Fig. 1 (3). Metabolic pathway for vinylidene chloride in mammals.

a) 1,1-dichloroethylene
b) chloroacetic acid
c) S-chlorocarbonylmethylcysteinyl-glutathione
d) S-carboxymethylcysteinylglutathione
e) N-acetyl-S-cysteinyl acetyl derivative
f) S-carboxymethylcysteine
g) thiodiglycollic acid
h) thioglycollic acid
j) dithioglycollic acid



a) 1,1-dichloroethylene
b) 1,1-dichloroethylene epoxide
c) 1,1-dichloroglycol
d) chloroacetyl chloride
e) dichloroacetaldehyde
f) chloroacetic acid

Fig. 2 (7). Metabolism of 1,1-DCE to monochloroacetic acid

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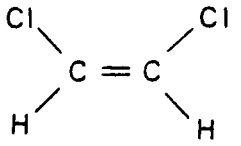
1,2- DICHLOROETHYLENE

$C_2H_2Cl_2$
Mol wt: 96.94 g/mole

cis-1,2-dichloroethylene



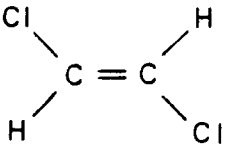
CAS: 000156592

Syn: cis-dichloroethylene;
cis-1,2-dichloroethene

bp: 60.3°C (at 760 mm Hg)

vp: 176.6 mm Hg (at 25°C)

trans-1,2-dichloroethylene



CAS: 000540590

Syn: trans-acetylene dichloride;
trans-dichloroethylene

bp: 47.5°C (at approx. 1 atm)

vp: 275.6 mm Hg (at 25°C)

Experimental data are limited regarding the metabolism of cis- and trans-1,2-dichloroethylene (1,2-DCE). However, several authors have postulated metabolic pathways for the compound by analogy to the metabolism of related compounds such as trichloroethylene.

The first step in 1,2-DCE metabolism is probably the formation of 1,2-dichloroethylene epoxide. The epoxide then undergoes rearrangement to yield another intermediate, dichloroacetaldehyde. Finally, the metabolic end products include chlorinated alcohol and acid compounds (1,2,3).

Leibman and Ortiz (1) proposed a metabolic scheme for 1,2-DCE as shown in Figure 1, based partly on the results of metabolism tests with isolated rat liver microsomal systems, and partly by analogy to the metabolism of other chlorinated ethylenes. The authors indicated that the metabolism of 1,2-DCE proceeds primarily via dichloroacetaldehyde. The aldehyde is produced mainly by rearrangement of the epoxide, involving migration of a chlorine atom from one carbon atom to the other. A similar chlorine-migration rearrangement may occur, to a lesser extent, with the dichloroethylene glycol (formed from hydration of the epoxide). Rearrangement of 1,2-DCE epoxide with migration of a hydrogen atom may yield monochloroacetyl chloride and ultimately produce monochloroacetic acid. Dichloroacetaldehyde and monochloroacetic acid were not identified in significant

quantities as end-product metabolites of 1,2-DCE by Leibman and Ortiz (1), however the authors suggest that the compounds are involved in the metabolic scheme.

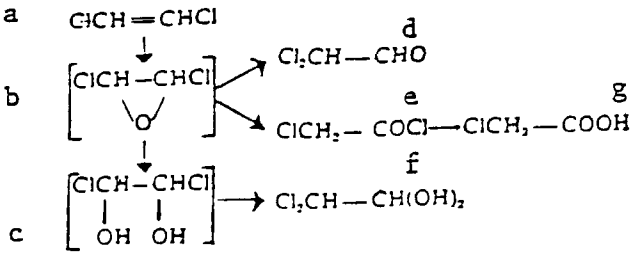


Fig. 1 (1). A proposed metabolic pathway of 1,2-dichloroethylene.

a) 1,2-dichloroethylene
b) 1,2-dichloroethylene epoxide
c) 1,2-dichloroglycol
d) dichloroacetaldehyde
e) monochloroacetyl chloride
f) 2,2-dichloro-1,1-ethanediol
g) monochloroacetic acid

Bonse et al. (3), reported the production of small amounts of dichloroacetic acid and dichloroethanol from rat liver preparations after perfusion with 55 nmol of cis- or trans-1,2-DCE per ml. After a review of the Bonse et al. study (3), Leibman and Ortiz (1) suggested that the identification of dichloroacetic acid and dichloroethanol as metabolites of 1,2-DCE probably indicates the formation of dichloroacetaldehyde as an intermediate.

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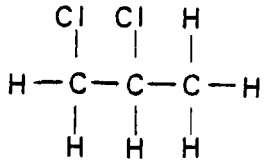
1,2-DICHLOROPROPANE

$C_3H_6Cl_2$



CAS: 000078875

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

Mol wt: 112.99 g/mole

bp: 96-37°C (at 760 mm Hg)

vp: 50.8 mm Hg (at 25°C)

Inhalation studies were conducted by Heppel et al. (1), in which blood levels of 1,2-dichloropropane were determined in rabbits and dogs. Rabbits (size, sex and number not specified) were exposed to constant concentrations of 2,200 or 1,500 ppm of dichloropropane in air for 7 hours per day for 5 days. Respective blood levels of 1.5 to 2.9 mg and 0.6 to 1.1 mg of dichloropropane per 100 cc of blood were found. Three dogs (size and sex not specified) were exposed to 1,000 ppm of dichloropropane for 7 hours, resulting in average blood levels of 1.3, 1.5 and 1.6 mg per 100 cc.

In related tests, Heppel et al. (1), concluded that rats, mice and guinea pigs excreted an unidentified pigment-producing substance in urine after exposure to dichloropropane vapors.

Hutson et al. (2), reported the rates and routes of 1,2-dichloropropane excretion in rats. In one experiment, 6 adult male and 6 adult female rats (Carworth Farm E strain) were administered, by stomach tube, one dose of 0.88 mg (8.5 uCi) of 1,2-dichloro(1-^{14}C)propane in 0.5 ml arachis oil. The excretion of radioactivity in urine and feces was then measured by scintillation at 24-hour intervals for 96 hours. After 96 hours the recovery of radioactivity by scintillation was also determined from the skin, alimentary tract and remaining carcass. Results of the experiment showed that radioactivity was excreted very rapidly, primarily in the urine. About 50.2% of the administered dose was excreted in urine in the first 24 hours. In decreasing order, less radioactivity was recovered from the feces, carcass, skin, and gut.

In a second experiment (2), the respiratory excretion of the compound was analyzed. A single oral dose of 1.07 mg (10.3 uc) of 1,2-dichloro-(1-^{14}C)propane was given to each of 5 female rats which were housed together in a compartmented chamber. Air was drawn through the chamber at the rate of 650 ml/min. and then collected in sodium hydroxide traps. Radioassays measured the amount of (^{14}C) carbon dioxide and other volatile radioactivity in the exhaled air.

Results of the respiration tests indicated that a large amount of radioactivity, 23.1% of the oral dose, was exhaled as volatile chlorinated hydrocarbon, probably as unchanged dichloropropane. In addition, 19.3% of the dose was expelled as (^{14}C) carbon dioxide, indicating that extensive metabolism of dichloropropane also occurred. The radioactive substances recovered in the tests were not identified in the report (2).

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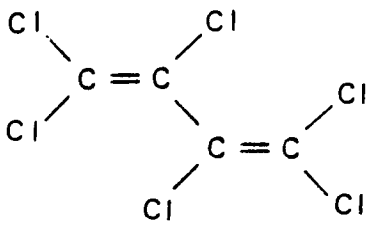
HEXACHLOROBUTADIENE

$C_4H_4Cl_6$



CAS: 000087683

Syn: HCBD

Mol. Wt.: 264.79 g/mole

bp: 210 - 220°C

vp: 22 mm Hg (at 100°C)

In a 1963 report, Murzakaev et al. (1), stated that the polychlorobutanes $C_4H_5Cl_5$ and $C_4H_4Cl_6$ are intermediate products in the metabolism of hexachlorobutadiene.

Gul'ko and Dranovskaya (2), utilizing a pulsed polarographic method, determined that mice fed hexachlorobutadiene (5 mg/kg) retained the following organ levels of the parent compound: liver, 17.4 and 28.8 ug, respectively, 1 and 2 hours after administration; brain, 14.5, 59.2 and 11.4 ug after 3, 24 and 96 hours, respectively.

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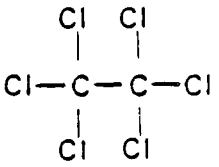
HEXACHLOROETHANE

C_2Cl_6



CAS: 000067721

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

Mol wt: 236.74 g/mole

bp: 186°C (at 777 mm Hg)

vp: 1.2 mm Hg (at 32.7°C)

Hexachloroethane (HCE) metabolism in rabbits was reported by Jondorf et al. (1). ^{14}C-Labelled hexachloroethane was fed to rabbits in doses of 0.5 g/kg. The results showed that HCE was metabolized very slowly. In three days, 5% of the radioactivity was detected in urine, 14% to 24% was measured in expired air, and the remainder was assumed to be located in the rabbit tissues and intestinal tract. Identification and concentrations of the urinary metabolites, shown as averages for three experiments, were reported as follows:

trichloroethanol, 1.3%
trichloroacetic acid, 1.3%
dichloroacetic acid, 0.8%
monochloroacetic acid (highly toxic), 0.7%
dichloroethanol, 0.4%
oxalic acid, 0.1%

The metabolites found in expired air included CO_2, hexachloroethane, tetrachloroethylene and 1,1,2,2-tetrachloroethane.

The metabolism of HCE by sheep was studied by Fowler (2) in a series of experiments. Following oral administration of 0.5 g HCE/kg to the sheep, samples of venous blood, urine, feces, bile and various tissue were taken periodically. Tetrachloroethylene (TCE) and pentachloroethane (PCE) were identified as the main metabolites. In the first experiment, blood levels of HCE, TCE and PCE peaked at 24 hours, at 10-28 ug/ml, 0.6-1.1 ug/ml, and 0.15-0.50 ug/ml, respectively. In a second experiment it was determined that most of the urinary and fecal excretion of HCE and its metabolites occurred within 24 hours. Greater amounts of each compound were eliminated in feces than in urine, as shown in Table 1. Results of a third experiment showed that the concentration of HCE in the bile was 8-10 times greater than the blood level. Analysis of tissue samples indicated that low levels of HCE and its metabolites were widely distributed throughout the animal.

Table 1. Total (ug) 24-hr excretion of HCE, TCE, and PCE in urine and feces of 2 anaesthetized sheep after oral administration of 0.5 g HCE/kg.

	Metabolite concentration (ug)	
	feces	urine
hexachloroethane	780-1260	50-70
tetrachloroethylene	854-1300	25-29
pentachloroethane	trace-468	20-25

In vitro experiments were also conducted by Fowler (2), using fresh liver slices in olive oil emulsion and 18 or 54 mg HCE/L. The tissue homogenates were incubated at 37°C for 4 hours. Both TCE and PCE were liberated during incubation. When the tests were repeated with liver slices heated for 5 minutes at 70°C prior to incubation, the two metabolites were liberated in much smaller amounts. The results indicated that the metabolism of HCE was an enzymatic process involving at least two enzymes, both of which were present in the liver.

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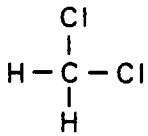
METHYLENE CHLORIDE

CH_2Cl_2



CAS: 000075092

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

Mol wt: 84.93 g/mole

bp: 40°C (at 760 mm Hg)

vp: 430.4 mm Hg (at 25°C)

The major metabolites of methylene chloride (CH_2Cl_2; dichloromethane) reported in the literature are carbon monoxide, carbon dioxide, and an unknown acid metabolite (1,2). No evidence was found to support the actual incorporation of methylene chloride into cellular constituents.

Several experimenters (3,4) have reported data that indicated formaldehyde (CH_2O) as a metabolite of methylene chloride. However, DiVencenzo and Hamilton (1) studied the fate of ^{14}C-labeled methylene chloride injected intraperitoneally in rats and suggested that the changes in CH_2O levels found in serum and tissue were physiologically induced; no evidence was found to support the conversion of CH_2Cl_2 to CH_2O in vivo.

Early investigations of the metabolism of methylene chloride suggested that it may be metabolized to carbon monoxide (5,6,7). Stewart et al. (5,6), exposed eleven volunteers to methylene chloride vapor in concentrations of 500 to 1,000 ppm for 1 or 2 hours. They found that the concentration of carbon monoxide (CO), in the form of carboxyhemoglobin (COHb), was increased in the blood of the subjects.

Kubic et al. (8), found that intraperitoneal administration of dihalomethane elevated carboxyhemoglobin in the blood of rats. In the same experiment the authors administered ^{13}C-dichloromethane to rats intraperitoneally at a dose of 3 mmol/kg. The infrared spectra of the blood of these rats showed the presence of the absorption band characteristic of ^{13}C-carbon monoxide. The authors considered this conclusive evidence that dichloromethane is metabolized to carbon monoxide in the rat. Other studies of dichloromethane metabolism in rats (1,2,9) using radioactive-labeled methylene chloride report findings consistent with those of Kubic et al. (8).

Several experimenters (9,10) have observed a maximum saturation of COHb in the blood after exposure to dichloromethane. Hogan et al. (10) exposed rats to 400 ppm dichloromethane, resulting in a 7% COHb level in the blood of the rats. Exposure levels as high as 2300 ppm caused no further increase in the 7% COHb level although the maximum COHb level persisted for a longer period at the higher doses. Similarly, Miller et al. (9) found that a dose of 3.0 mmol/kg injected intraperitoneally in rats yielded a maximum level of COHb blood saturation of about 6%.

Kubic and Anders (11) found that dihalomethanes are metabolized to carbon monoxide by hepatic microsomal fractions in the presence of NADPH and oxygen. An increased rate of conversion of dibromomethane to CO was correlated with increased microsomal cytochrome P-450 content, indicating a cytochrome P-450-dependent mixed oxidase system. Hogan et al. (10) reported similar findings using dichloromethane.

DiVencenzo and Hamilton (1) studied the disposition of (^{14}C) methylene chloride injected intraperitoneally in rats. Each rat received from 11.7 to 21.6 uCi of radioactivity in doses from 412 to 930 mg of $^{14}CH_2Cl_2$ per kg body weight. After two hours, 75% of the radioactivity was exhaled.
After 24 hours a total of 98% of the initial dose was exhaled. Urinary radioactivity accounted for about 1% of the dose at 24 hours. Fecal radioactivity was less than 0.1% at 24 hours (Table 1).

Of the radioactivity collected from the breath, unchanged $^{14}CH_2Cl_2$ accounted for 98.8% of breath radioactivity at 2 hours, 96.1 at 8 hours, and 93% at 24 hours. At 24 hours, less than 7% of the radioactive dose was in the form of metabolites: 2% was converted to ^{14}CO, 3% was converted to $^{14}CO_2$, and 1% was an unknown compound (Table 2). According to the authors, CO may be an intermediate in the formation of CO_2 (1).

Table 1 (1). Dissemination of radioactivity in rats treated intraperitoneally with (^{14}C)methylene chloride[a]

	Experimental Duration					
	2 hr[b]	N	8 hr	N	24 hr[b]	N
Breath	77.9, 93.2	2	98.6, 96.8	2	98.2	1
Urine	0.01	4	0.01	2	1.06 ± 0.15	5
Feces	0.01	4	0.01	2	0.07 ± 0.01	5
Carcass	3.09 ± 0.99	4	2.06, 2.42	2	1.53 ± 0.12	3
Chamber washings	0.12 ± 0.08	4	0.41, 0.15	2	0.07 ± 0.04	5
Total	88.8		100.2		100.9	

[a] (^{14}C)Methylene chloride was administered i.p. in doses ranging from 412-930 mg/kg. Values are expressed as percent of dose.
[b] Mean ± SE

Table 2 (1). Radioactive compounds detected in rat breath following the intraperitoneal administration of (^{14}C)methylene chloride[a]

Compound	Experimental Duration					
	2 hr	N	8 hr	N	24 hr	N
CH_2CL_2	77.0, 92.0[b]	2	95.3, 92.6[b]	2	91.50	1
CO_2	0.44, 0.65	2	1.44, 1.61	2	3.04	1
CO	0.14, 0.14	2	1.16, 1.69	2	2.15	1
Unknown	0.34, 0.46	2	0.74, 0.86	2	1.49	1

[a] Expressed as percentage of the original dose.
[b] Individual values for each experimental animal.

DiVencenzo and Hamilton (1) found the amount of radioactivity in the rat tissues to be relatively low, less than 2% of the dose after 24 hours. The liver, kidneys, and adrenal glands had the highest amount, although the radioactivity was generally widespread in the rat tissues. No metabolites other than ^{14}CO, $^{14}CO_2$, and an unknown compound were found in the breath, blood or tissues.

Rodkey and Collison (2), using a closed rebreathing system, exposed rats to 0.2 mmol of $^{14}CH_2Cl_2$ vapor per kg for 15 hours. Expired ^{14}CO and $^{14}CO_2$ accounted for 76% of the radioactivity given. They found no accumulation of radioactivity in the tissues at these low doses.

In a study of the metabolism of ^{14}C-labelled methylene chloride in rats, Carlsson and Hultengren (12) found that immediately after exposure to 1,935 mg of $^{14}CH_2Cl_2$ per m^3 of inspiratory air, adipose tissue contained the highest level per gram of tissue (Figure 1). In the follow-up study (6 hours after exposure) it was found that radioactive carbon decreased very rapidly in the adipose tissue and the brain tissue. Levels in other tissues (liver, kidney, and adrenals) declined at slower rates.

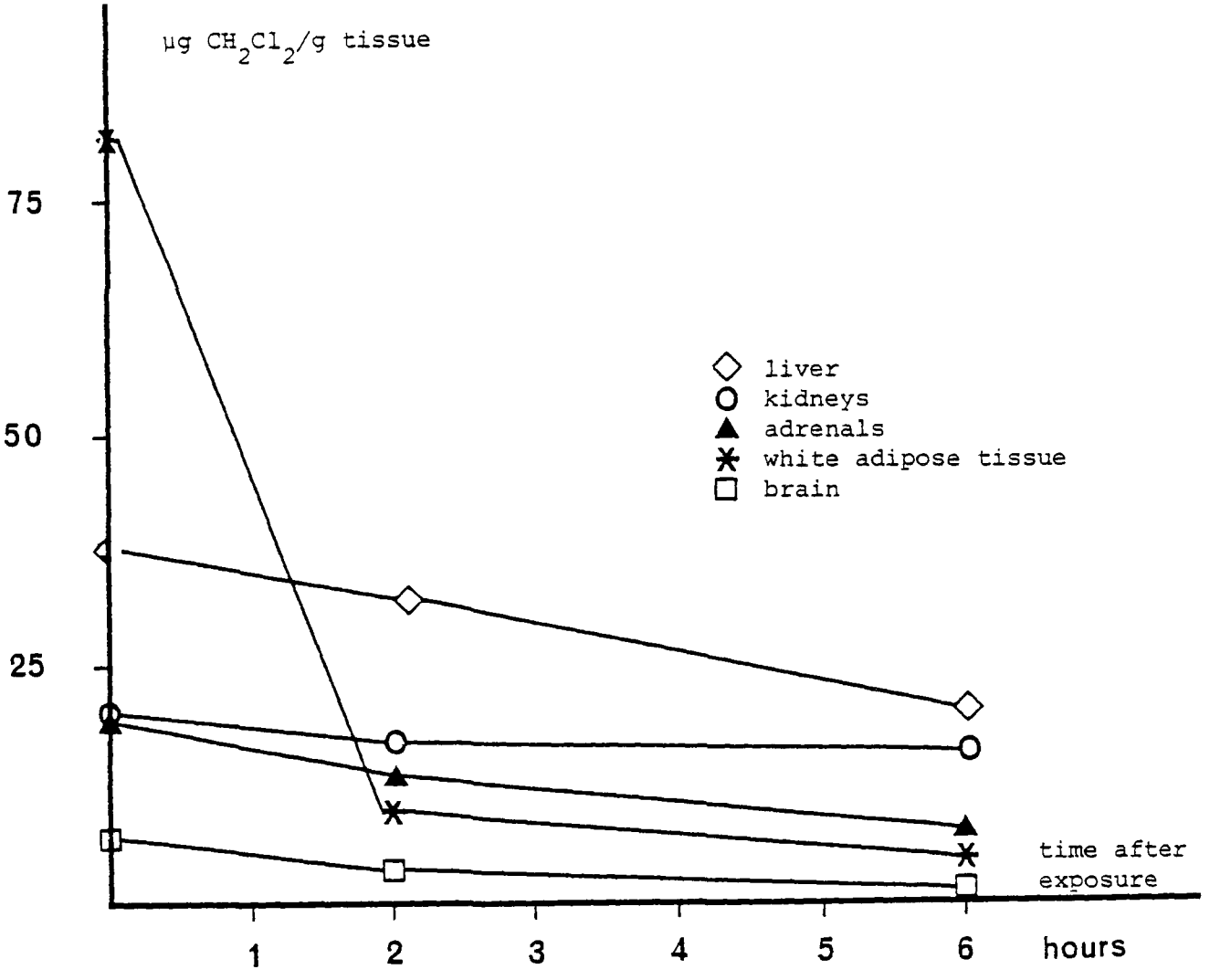


Figure 1. Accumulation of methylene chloride (µg CH_2Cl_2/g tissue) and its metabolites in organs and tissues during the 6-h follow-up after exposure to methylene chloride in inspiratory air. (Redrawn from 12)

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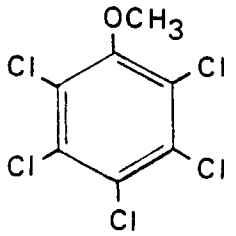
PENTACHLOROANISOLE



$C_7H_3Cl_5O$

CAS: 1825-21-4

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

Mol. wt.: 280.34 g/mole

The uptake, metabolism, and elimination of pentachloroanisole (PCA) in rainbow trout was reported by Glickman et al.(1). PCA uptake was studied in fish (8-10 g) exposed to 0.024 mg of (^{14}C)PCA per liter of water for a total of 12 hours. Samples of blood and tissues (liver, muscle, and fat) were collected periodically during exposure for analysis of PCA concentrations. From the data collected it was determined that PCA was rapidly taken up from water and was especially concentrated in adipose tissue. The concentration of PCA in adipose tissue reached a level equal to 4,000 times the initial PCA concentration in water.

In the elimination tests, fish were exposed for 12 hours to (^{14}C)PCA (0.024 mg/L) and then removed to fresh water. The analysis of samples taken daily for 7 days showed very long retention of PCA in the blood and tissues. The half-life of PCA was calculated for the samples and expressed in terms of days as follows: fat tissue, 23.4; liver, 6.9; muscle, 6.3; and blood, 6.3. The long retention times were attributed to high lipid solubility of PCA.

Metabolism experiments were conducted with rainbow trout (50-100 g) exposed to 0.05 mg (^{14}C)PCA/L at 12°C for 24 hours. After exposure, the bile, liver, and muscle tissues were collected for determination of metabolites. Analysis revealed only PCA in muscle tissue, PCA plus a more polar substance in liver tissue, and a polar metabolite in bile which was identified as glucoronide-conjugated pentachlorophenol (PCP). Through further experimentation the authors concluded that the PCP detected in bile was formed in vivo by demethylation of PCA.

Based on their results, Glickman et al.(1), suggested two explanations of the route and rate of PCA elimination from rainbow trout. First, biliary excretion of the compound may be controlled by the rate of PCA demethylation to PCP, which is then conjugated with glucoronic acid and excreted. Secondly, the transfer of PCA from the tissues to the metabolic and excretory sites (liver, kidney, and gills) may be the overall factor influencing PCA elimination.

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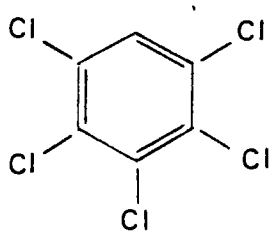
1. Glickman, A. H., C.N. Statham, A. Wu, and J.J. Lech. 1977. Studies on the uptake, metabolism, and disposition of pentachlorophenol and pentachloroanisole in rainbow trout. Toxicol. Appl. Pharmacol. 41:649-658.

PENTACHLOROBENZENE

C_6HCl_5



CAS: 000608935

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

Mol. Wt.: 250.34

bp: 277 (at 760 mm Hg)

vp: 1.04 mm Hg (at 98.6°C)

Parke and Williams (1) reported that pentachlorobenzene is only slightly altered in vivo by rabbits. Urinary excretion of metabolites by the rabbit plays a minor role in bodily elimination of pentachlorobenzene, accounting for not more than 1% of a 0.5 mg/kg dose. Three to four days following gavage administration, 60% of the dose was isolated in the gut contents and tissues. Additionally, 10-20% of the dose was deteted in expired air as lesser chlorinated benzenes.

Kolhi et al. (2), reported that analysis of urine and feces obtained from rabbits (4-5 kg) for 10 days following ip administration of pentachlorobenzene (300 mg), revealed the presence of pentachlorophenol (1% of dose), 2,3,4,5-tetrachlorophenol (1% of dose) and a trace amount of bound metabolites. The presence of urinary dechlorination products led Kolhi et al. (2), to propose that the oxidation and accompanying dechlorination-hydroxylation of pentachlorobenzene may be associated with an arene oxide intermediate.

Following daily oral dosing of pentachlorobenzene (8 mg/kg) to male rats (250 g) for 19 days, Engst et al. (3), identified the following metabolites:

A. Urine:

1) 2,3,4,5-tetrachlorophenol and pentachlorophenol, identified as the main metabolites

2) pentachlorobenzene, 2,3,4,6-tetrachlorophenol and/or 2,3,5,6-tetrachlorophenol, present in free form

3) 2,4,6-trichlorophenol and 1,2,3,4-tetrachlorophenol, present in small amounts

B. Feces:
pentachlorobenzene, tetrachlorobenzene and trichlorobenzene

C. Kidneys and blood:
pentachlorophenol and 2,3,4,5-tetrachlorophenol

D. Liver:
pentachlorobenzene and 1,3,5-trichlorobenzene.

Leber et al. (4), reported in 1977 the results of a metabolism study in which rhesus monkeys were given ^{14}C-labelled pentachlorobenzene (20 mg/animal). Up to 22% of the dose was isolated from the feces and urine during the first 6 days following dosing. Feces were found to contain the parent compound while the radioactive compounds in the urine were identified as two isomers of tetrachlorophenol. The authors concluded that pentachlorobenzene exhibits a prolonged retention time in the rhesus monkey (4).

Following a single ip injection of pentachlorobenzene (403 uM/kg) to female rats, Koss and Koransky (5) analyzed the urine and feces collected for 4 days to identify the metabolic products. Almost complete biodegradation of the pentachlorobenzene was observed; the major portion of the dose was excreted in the urine and feces as hydrophilic metabolites, including pentachlorophenol (9%), 2,3,4,5-tetrachlorophenol, tetrahydroquinone, a hydroxylated chlorothiocompound, and trace amounts of another tetrachlorophenol isomer. These compounds were also identified in the tissues of the treated rats.

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2. Kolhi, J., D. Jones and S. Safe. 1976. The metabolism of higher chlorinated benzene isomers. Can. J. Biochem. 54(3): 203-8.

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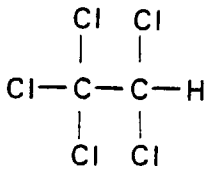
PENTACHLOROETHANE

C_2HCl_5



CAS: 000076017

Syn: ethane pentachloride

Mol wt: 202.30 g/mole

bp: 162°C (at 760 mm Hg)

vp: 4.5 mm Hg (at 25°C)

The metabolism of pentachloroethane (PCE) in mice was studied extensively by Yllner (1). Female albino mice were injected subcutaneously with 20 uL of PCE and were sustained on a 5% glucose solution during the studies. Urine, feces, and expired air were collected for 4 days. Quantitative determinations of PCE metabolites were made by gas and paper chromatography.

About 80% of the administered dose of PCE was accounted for in 4 days. The greatest excretion of metabolites occurred in the first 24 hours after injection. In order of predominance, the metabolites were identified as PCE (unchanged), trichloroethanol, trichloroacetic acid, tetrachloroethylene, and trichloroethylene. Fowler (2) also identified tetrachloroethylene as a metabolite of PCE given orally to sheep. The results of Yllner's studies (1) indicated that hydrolysis of the carbon-to-chlorine bond was the major and most rapid reaction in PCE metabolism. Hydrolysis of C-Cl bonds apparently yielded chloral, an important intermediate in the formation of trichloroethanol by reduction and trichloroacetic acid by oxidation. The metabolites trichloroethylene and tetrachloroethylene were probably formed by direct removal of chlorine and hydrochloric acid, respectively, from chloral.

In more recent studies, Yllner (3) confirmed his preliminary data on the metabolism of PCE in mice. PCE (1.1 - 1.8 g/kg) was injected subcutaneously in mice and excretion was monitored for 3 days. Specific quantitative determinations of the metabolites showed that about 1/3 (12 - 51%) of the injected dose was expired unchanged. The levels of other metabolites were reported as follows:

trichloroethanol	16-32%	in urine
trichloroacetic acid	9-18%	in urine
trichloroethylene	2-16%	in expired air
tetrachloroethylene	3-9%	in expired air.

In addition to the above mentioned pathway of PCE metabolism, Yllner (3) suggested that at least part of the urinary metabolites (trichloroethanol and trichloroacetic acid) were probably formed via trichloroethylene and its metabolite, chloral hydrate.

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1. Yllner, S., 1963. The metabolism of pentachloroethane and unsymmetric tetrachloroethane. Proc. XIV. Int. Congr. Occupat. Health. Madrid. 825-827.

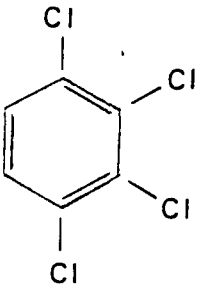
2. Fowler, J.S.L., 1969. Some hepatotoxic actions of hexachloroethane and its metabolites in sheep. Brit. J. Pharmacol. 35(3):530-542.

3. Yllner, S., 1971. Metabolism of pentachloroethane in the mouse. Acta pharmacol. et toxicol. 29(5-6):481-489.

TETRACHLOROBENZENE

$C_6H_2Cl_4$

Mol wt: 215.88g/mole



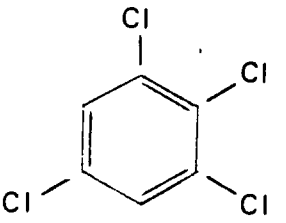
1,2,3,4-tetrachlorobenzene

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)



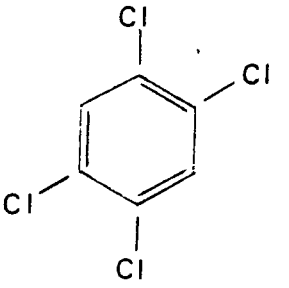
1,2,3,5-tetrachlorobenzene

CAS: 000634662

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: 243-6°C (at 760 mm Hg)

vp: 0.1 mmHg (at 25°C)

In a study reported in 1958, Jondorf and colleagues (1) examined the metabolism of the three isomeric forms of tetrachlorobenzene in doe chinchilla rabbits. Each experimental rabbit received a daily dose (0.3 or 0.5 g/kg), via gavage administration, of one of the isomeric tetrachlorobenzenes. Expired air, urine and feces were collected daily for spectrophotometric and chromatographic determination of parent compound and metabolite concentrations. At the end of 6 days, some of the experimental

rabbits were sacrificed for tissue and organ analysis. Results of the tests are presented in Tables 1-4 (1).

Table 1. *Elimination of unchanged tetrachlorobenzenes in the expired air of rabbits receiving these compounds orally*

Tetrachlorobenzene fed	Dose (g./kg.)	Percentage of dose in expired air: Days after dosing 1	2	3	4	5	Total
1:2:3:4-	0·5	1·9	2·2	1·6	0·2	—	5·9
	0·3	0·8	1·7	6·7	—	—	9·2
1:2:3:5-	0·5	2·1	2·1	1·2	2·9	2·6	10·9
	0·3	0·9	3·2	9·8	—	—	13·9
1:2:4:5-	0·5	1·2	0·2	0·2	—	—	1·6

Table 2. *Tetrachlorobenzenes in tissues*

Dose, 0·5 g./kg. orally. Rabbits were killed 6 days after dosing.

Tetrachlorobenzene fed	Percentage of dose found unchanged in: Liver	Brain	Skin	Depot fat	Gut contents	Rest of body	Total
1:2:3:4-	0·1	—	2	5	0·5	2·0	10
1:2:3:5-	<0·5	<0·2	5	11	1·4	5·2	23
1:2:4:5-	0·1	<0·1	10	25	6·2	6·4	48

Table 3. *Urinary excretion of the metabolites of tetrachlorobenzenes*

Dose, 0·5 g./kg. orally. Figures given are mean values with ranges in parentheses and the number of experiments indicated by superior figures.

Tetrachlorobenzene administered	Percentage of dose excreted as: Glucuronide	Ethereal sulphate	Mercapturic acid	Tetrachlorophenol: Free	Tetrachlorophenol: Total
1:2:3:4-	30 (22–36)[5]	3 (1–8)[5]	<1[5]	8 (7, 9)[2]	43 (38, 48)[2]
1:2:3:5-	6* (2–10)[9]	2 (1–6)[9]	0[3]	1·9 (1·2, 2·5)[3]	5 (4, 6)[2]
1:2:4:5-	4† (1–8)[11]	1 (<1–2)[11]	0[3]	1·3 (0·9, 1·6)[2]	2·2 (1·1, 3·2)[2]

* Without collars, 5·5 (2–8)[6]; with collars, to prevent coprophagy, 6 (4–10)[3].
† Without collars, 2 (<1–8)[6]; with collars, 4 (3–6)[3]. Ethereal sulphate values were not significantly different with or without collars.

Table 4. *Summary of excretion of metabolites of the isomeric tetrachlorobenzenes*

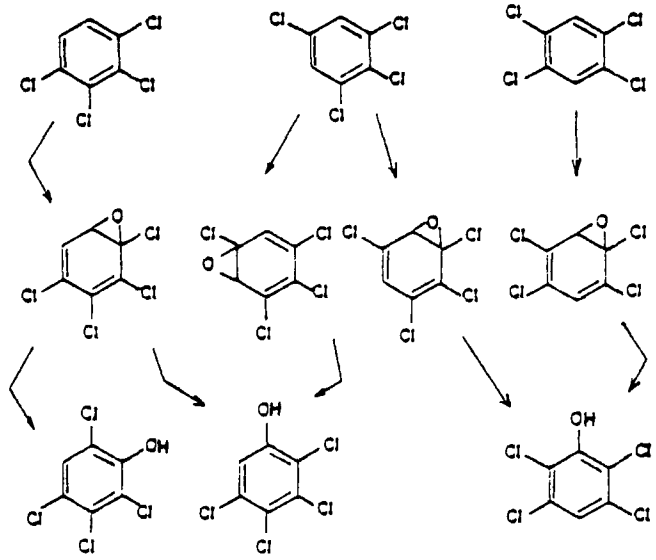
Dose, 0·5 g./kg. orally. Figures are mean values of two or three experiments covering excretion during 6 days after dosing.

Tetrachlorobenzene fed	Percentage of dose eliminated as: Phenols: Tetrachlorophenols	Phenols: Other phenols	Unchanged tetrachlorobenzene in: Faeces	Unchanged tetrachlorobenzene in: Tissues	Unchanged tetrachlorobenzene in: Breath	Other chlorobenzenes in breath	Total
1:2:3:4-	43	<1	5	10	8	2	68
1:2:3:5-	5	5	14	23	12	9	68
1:2:4:5-	2	5	16	48	2	10	83

As shown in the tables, metabolism of the tetrachlorobenzenes proceeded fairly slowly. In 6 days 43% of 1,2,3,4-tetrachlorobenzene was oxidized to 2,3,4,5-tetrachlorophenol, 5% of 1,2,3,5-tetrachlorobenzene was oxidized to 2,3,4,6-tetrachlorophenol, and 2% of 1,2,4,5-tetrachlorobenzene was oxidized to 2,3,5,6-tetrachlorophenol. Two to 15% of the administered compounds was dechlorinated and excreted in the expired air and urine as less

chlorinated benzenes, while the reminder was excreted or retained in the tissues unchanged (1).

Kohli et al. (2), also studied the metabolism of tetrachlorobenzenes in rabbits. In addition to those isolated by Jondorf et al. (1), the phenolic metabolites of 1,2,3,4-tetrachlorobenzene were found to contain 2,3,4,6-tetrachlorophenol, and 2,3,4,5- and 2,3,5,6-tetrachlorophenol for 1,2,3,5-tetrachlorobenzene (2). They suggested that the conversion to tetrachlorophenols involves the formation of arene oxide intermediates, as shown in the following diagram.



Metabolism of isomeric tetrachlorobenzenes

References

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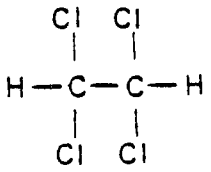
1,1,2,2-TETRACHLOROETHANE

$C_2H_2Cl_4$



CAS: 000079345

Syn: acetylene tetrachloride; dichloro-2,2-dichloroethane; tetrachloroethane; sym-tetrachloroethane; TCE.

Mol wt: 167.84 g/mole

bp: 760°C (at 146.5 mm Hg)

vp: 6.4 mm Hg (at 25°C)

The literature on 1,1,2,2-tetrachloroethane (tetrachloroethane) metabolism is limited with regard to biotransformation in humans. However, Yllner (1) conducted a comprehensive study of tetrachloroethane metabolism in the mouse. Also, a thorough review of the available literature is included in the NIOSH criteria document on occupational exposure to 1,1,2,2-tetrachloroethane (2).

The retention and elimination of tetrachloroethane and other halogenated hydrocarbons by humans was studied by Morgan et al. (3). Subjects were administered about 2.5 mg of ^{38}Cl-labelled 1,1,2,2-tetrachloroethane in a single-breath inhalation exposure, in which each subject held the vapor in his lungs for 20 seconds to maximize pulmonary absorption. From analysis of ^{38}Cl-activity in expired breath immediately after exposure, it was determined that approximately 97% of the tetrachlorethane was retained in the lungs. The elimination of ^{38}Cl-activity in expired air was then measured for 1 hour. Results showed that only 3.3% of the retained tetrachloroethane was exhaled in one hour, indicating a low rate of pulmonary elimination for the compound (2,3). In addition, a urine sample was taken 1 hour after administration of the hydrocarbon and measurement of the radioactivity demonstrated that tetrachloroethane had a relatively high urinary excretion rate (equivalent to 0.015% per minute) compared to the other hydrocarbons tested (3).

Morgan et al. (3), also performed in vitro tests to determine the partition coefficients (K_D) of 1,1,2,2-tetrachloroethane between blood and air and between serum and air. Samples of 2 ml of venous blood or serum were equilibrated with 1 ml of tetrachloroethane for 5 minutes at 40°C. The K_D values, defined as the concentration in liquid/ concentration in gas, were reported as 72.6 (blood/air) and 78.2 (serum/air). The authors suggested that the high K_D values for tetrachloroethane represented the compound's solubility in blood and serum lipids, which would account for its high level of retention in the lungs (2,3).

The pattern of elimination, identification of metabolites, and probable metabolic pathways were reported by Yllner (1) in an extensive study of 1,1,2,2-tetrachoroethane metabolism in the mouse. Mice were injected intraperitoneally with 0.21-0.32 g of ^{14}C-labelled tetrachloroethane (0.51 uCi/mg) per kg of body weight, and the elimination of radioactivity was measured by liquid scintillation spectrometry for 3 days. Metabolites in urine and expired air were determined by gas or paper chromatography and isotope dilution analysis (1,2).

The results showed that the metabolism of 1,1,2,2-tetrachloroethane in the mouse was fairly rapid and complete, 60-70% of the dose being excreted in 24 hours. In 3 days, about 50% of the administered dose was oxidized and expired as $^{14}CO_2$. Less than 4% was expired unchanged, 28% was excreted in urine, less than 1% was detected in feces contaminated with urine, and 16% of the dose remained in the animal tissues (1,2).

Analysis of the expired air revealed the presence of minute quantities of trichloroethylene and tetrachloroethylene in addition to CO_2 and unchanged tetrachloroethane. In the first 24 hours, tri- and tetrachloroethylene were expired in amounts equal to about 0.2 - 0.4% of the injected dose of 1,1,2,2-tetrachloroethane (1).

The urinary metabolites excreted in 24 hours were identified and expressed as percentages of urinary radioactivity as shown in Table 1 (1).

	% of urinary activity	
	Mean[a]	Range
Dichloroacetic acid	27(7)	20-34
Trichloroacetic acid	4(4)	2-8
Trichloroethanol	10(5)	3-15
Oxalic acid	7(7)	5-10
Glyoxylic acid	0.9(4)	0.4-1.4
Urea	2(2)	2-3

[a] The figures in brackets denote the number of animals examined.

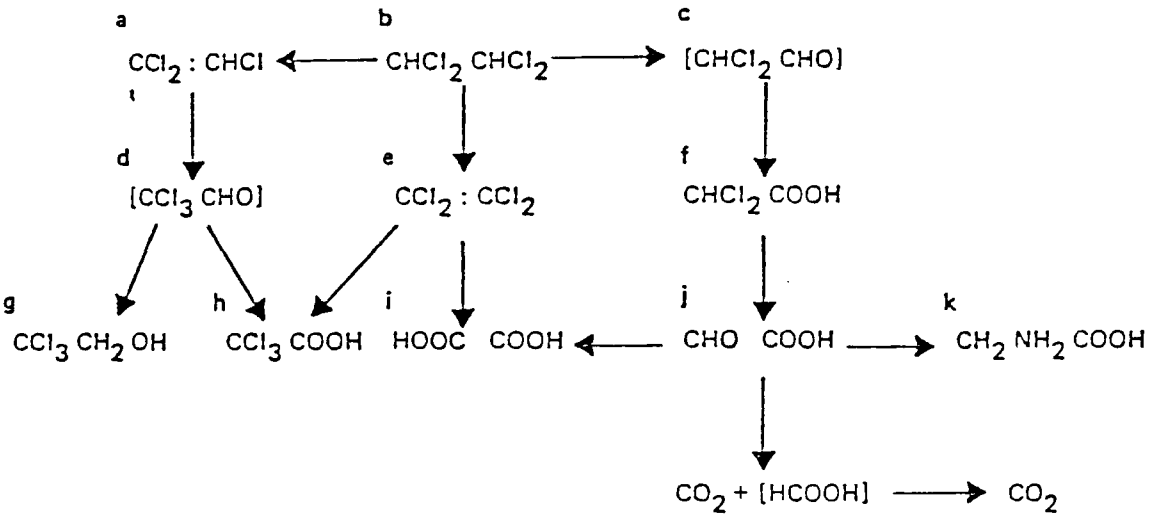
Table 1 (1). Isotope dilution analysis of urinary metabolites from mice receiving 1,1,2,2-tetrachloroethane ^{14}C. Dose 0.16 - 0.32g/kg. Percentage of urinary activity excreted in 24 hours.

Ikeda and Ohtsuji (4) also reported low levels of the urinary metabolites trichloracetic acid and trichloroethanol in rats, following exposure to 1,1,2,2-tetrachloroethane. Two studies were conducted, and urinary concentrations of total trichloro-compounds (TTC), trichloroacetic acid (TCA), and trichloroethanol (TCE) were determined for each by a modification of the Fujiwara color reaction method. In the first experiment, rats were exposed to 200 ppm of tetrachloroethane for 8 hours. Urine was collected for 48 hours and the concentrations of TTC, TCA, and TCE were determined to be 8.2, 1.7, and 6.5 mg/kg of body weight, respectively. The second test involved intraperitoneal injection in rats of 2.78 mmol of tetrachloroethane per kg body weight. In the first 48 hours after injection, urinary metabolite concentrations were reported to be 2.1 mg/kg TTC, 1.3 mg/kg TCA, and 0.8 mg/kg TCE. In the next 48-hour period the respective metabolite levels were 0.3, 0.3, and an immeasurable amount. The authors pointed out that among tetrachloroethane and the other compounds tested (trichloro- and tetrachloro-deriviatives of ethane and ethylene), variations in the quantities of metabolites eliminated were related to the vapor pressure of the test compounds. Furthermore, it was stated that the rate of elimination is determined in part by the compound's degree of stability, or tendency to undergo biotransformation (2,4).

Yllner (1) proposed a scheme for the metabolism of 1,1,2,2-tetrachloroethane, shown in Figure 1, based on the study of tetrachloroethane metabolism in the mouse. The major pathway probably involves hydrolytic cleavage of the two carbon-chlorine bonds to form dichloroacetaldehyde hydrate, which is then oxidized to the major intermediate metabolite, dichloroacetic acid. Dichloroacetic acid, not a stable end product, undergoes further biotransformation, probably via hydrolytic dehalogenation, to produce the urinary metabolite glyoxylic acid (1,2). The degradation of 1,1,2,2-tetrachloroethane to glyoxylic acid was substantiated by the detection of CO_2 and oxalic acid, which are glyoxylate metabolites, in mice exposed to tetrachloroethane (1). The production of glycine, another end product of glyoxylic acid, was demonstrated by the excretion of large amounts of hippuric acid from mice following simultaneous injections of ^{14}C-tetrachloroethane and sodium benzoate (1,2).

A second metabolic pathway was described in which a minor amount of 1,1,2,2-tetrachloroethane is probably dechlorinated by a non-enzymic reaction to form trichloroethylene, the precursor to the urinary metabolites trichloroacetic acid and trichloroethanol (1,2).

Third, a very small amount of 1,1,2,2-tetrachloroethane probably undergoes oxidation to tetrachloroethylene, which the author suggested would contribute slightly to the production of the urinary end products oxalic acid and trichloroacetic acid, based on the results of an earlier study (Yllner, S., 1961, Nature, 191: 820) on the metabolism of tetrachloroethylene (1,2).



a) trichloroethylene
b) tetrachloroethane
c) dichloroacetaldehyde
d) trichloroacetaldehyde
e) tetrachloroethylene
f) dichloroacetic acid
g) trichloroethanol
h) trichloroacetic acid
i) oxalic acid
j) glycine acid
k) glyceine

Fig. 1. Proposed metabolic pathways of 1,1,2,2-tetrachoroethane. The bracketed compounds were not isolated. From the NIOSH criteria document on occupational exposure to 1,1,2,2-tetrachloroethane (2) as adapted from Yllner (1).

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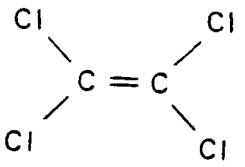
TETRACHLOROETHYLENE

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/mole

bp: 121°C (at 760 mm Hg)

vp: 18.0 mm Hg (at 25°C)

Various researchers have reported on the metabolites of tetrachloroethylene. Much of what has been reported is contradictory. The conflicting data involves the identification of metabolites found in the urine. Researchers of the metabolism of tetrachloroethylene in animals and humans agree that trichloroacetic acid is a metabolite in the urine. Daniel (1), Bonse et al. (2), Leibman and Ortiz (3), and Hake et al. (4) report that trichloroacetic acid is the only metabolite of tetrachloroethylene found in the urine. Several experimenters have found oxalic acid as a metabolite in the urine (5,6). Ikeda et al. (7,8) found trichloroethanol. Ogata et al. (9) found an unknown chlorinated hydrocarbon that gave trichloroacetic acid upon oxidation but could not identify it as trichloroethanol. One researcher (6) reported ethylene glycol as the most prevalent metabolite.

Yllner (5) exposed mice to ^{14}C-tetrachloroethylene vapor (1.3 mg/gm body weight). Using chromatographic, autoradiographic and isotope-dilution methods, he found the following: 52% of the total urinary ^{14}C-activity was identified as trichloroacetic acid, oxalic acid accounted for 11%, and dichloroacetic acid was found in trace amounts. No trichloroethanol was found. Yllner was unable to extract 18% of the urinary ^{14}C-activity. To account for the trichloroacetic acid he proposed the formation of an epoxide intermediate as one metabolic pathway. The epoxide then undergoes rearrangement to form trichloroacetic chloride, as shown:

$$Cl_2C{=}CCl_2 \rightarrow Cl_2C\overset{O}{\frown}CCl_2 \rightarrow Cl_3C-COCl \rightarrow Cl_3C-COOH$$

Daniel (1), studying the distribution of ^{36}Cl-tetrachloroethylene radioactivity fed to rats, detected trichloroacetic acid and inorganic chloride as the only metabolites of tetrachloroethylene in urine. He found an equimolar ratio between trichloroacetic acid and chloride ion. Therefore, little if any oxalic acid could have been present. Daniel (1) suggested that the metabolism of tetrachloroethylene may involve the following series of reactions:

$$Cl_2C{=}CCl_2 \rightarrow Cl_2C\overset{O}{\diagup\diagdown}CCl_2 \rightarrow Cl_3C-COCl \rightarrow Cl_3CCOOH + Cl^-$$

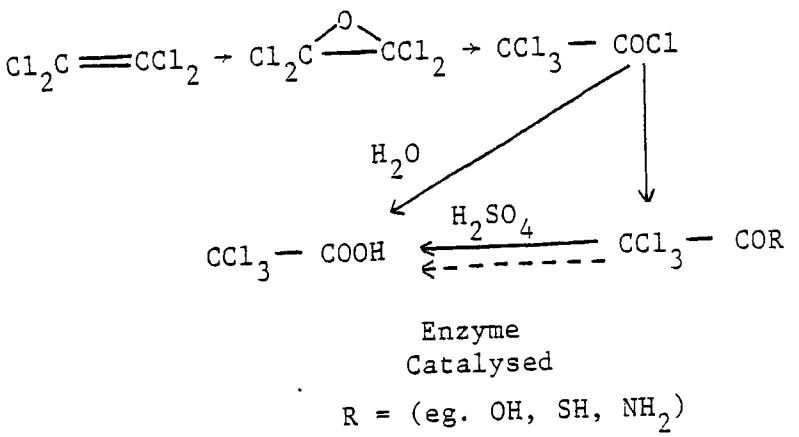
In this proposed pathway, the acid chloride is rapidly hydrolized to trichloroacetic acid. Neither trichloroethanol or oxalic acid are formed.

Ikeda and Ohtsuji (7) exposed rats to tetrachloroethylene vapor at a concentration of 200 ppm for 8 hours and collected the urine for 48 hours from the start of exposure. They determined the metabolites colorimetrically by the Fujiwara reaction and found trichloroacetic acid and trichloroethanol as the urinary metabolites of tetrachloroethylene. In the same report Ikeda and Ohtsuji (7) found that male workers exposed to 20-70 ppm and 200-400 ppm tetrachloroethylene excreted both trichloroethanol and trichloroacetic acid in the urine. In order to determine the effects of different routes of administration on the urinary metabolites Ikeda and Ohtsuji (7) injected tetrachloroethylene intraperitoneally into rats and mice. The urine was collected for 48 hours after injection. They found little or no trichloroethanol excreted in the urine of the rats and mice.

Ogata et al. (9) exposed human male volunteers to 87 ppm tetrachloroethylene for 3 hours, collecting the urine frequently for up to 100 hours after the start of exposure. Two trichloro-compounds were determined, trichloroacetic acid and an unknown compound which gave trichloroacetic acid upon oxidation by chromium oxide. Ogata et al. (9) could not detect the absorption maximum of trichloroethanol after treating with beta-glucuronidase, so the unknown chlorinated hydrocarbon could not be shown to be trichloroethanol.

Dmitrieva (6) reported that ethylene glycol was the most prevalent urinary metabolite in rats following acute and chronic exposure to tetrachloroethylene. Trichloroacetic acid and oxalic acid were also found.

Bonse et al. (2), studying oxirane formation and biological reactivity of chlorinated ethylenes, found that in isolated perfused rat livers, trichloroacetic acid was the only metabolite of tetrachloroethylene. Ten to 15% of the total uptake of tetrachloroethylene was found as trichloroacetic acid in the circulating perfuse, and 3 to 5% of the total uptake was found as trichloroacetic acid bound to the liver tissue and extractable only after acid hydrolysis. The authors proposed the following mechanism based on their findings:



The authors postulated that trichloroacetyl chloride reacted with cell constituents resulting in acylation (2).

In a review of the literature, Liebman and Ortiz (3) proposed that tetrachloroethylene is metabolized to tetrachloroethylene oxide by mixed function oxidation followed by hydration of the epoxide, forming a glycol. Due to the symmetry of the epoxide and the glycol, rearrangement of either would yield only one product, trichloroacetyl chloride, which is hydrolyzed to trichloroacetic acid.

Whether the different metabolites are due to differences in experimental procedure or method of analysis is not fully explored in the literature. Daniel (1) stated that some of the conflicting observations may be due to the different routes of administration employed. Ikeda and Ohtsuji (7) suggested that the differences may be due to duration and intensity of exposure. Leibman and Ortiz (3), in a review of the metabolism of halogenated ethylenes, suggest that in those studies (7,8) using the Fujiwara colorimetric reaction, it was assumed that trichloroethanol was that part of the total trichloro compounds not identified as trichloroacetic acid. Ogata et al. (9), using this method, could not prove that trichloroethanol was part of the total trichloro compounds.

Studies on the fate of tetrachloroethylene in rats and humans indicate that the greater part of the dose (by inhalation, ingestion, or intraperitoneal injection) is expired via the lungs (1,5,9,10,11). Daniel (1) fed rats 1.75 uCi ^{36}Cl-tetrachloroethylene and found that 97.9% of the original dose was expired in 48 hours. None of the metabolites of tetrachloroethylene were found in the expired air. ^{36}Cl-Tetrachloroethylene was expired by the rats unchanged. Approximately 2% of the radioactivity was excreted in the urine in 18 days. Of this, trichloroacetic acid in the urine made up 0.6% of the original radioactivity.

Yllner (5) exposed mice to ^{14}C-tetrachloroethylene vapor (1.3 mg/gm body weight) in sealed flasks. Seventy percent of the solvent was absorbed. In four days about 90% of the absorbed ^{14}C-activity was excreted: 70% of the absorbed ^{14}C-activity was found in expired air, 20% in the urine, and less than 0.5% in the feces. After exposure of human volunteers to 87 ppm for 3 hours, Ogata et al. (9), found that 1.8% of the inhaled amount was excreted by the kidney as trichloroacetic acid. Other researchers (10,12) have observed that only a small portion of the solvent accumulated in the body, while most of the solvent was rapidly absorbed and excreted via the lungs. Bolanowska and Golacka (13) reported results contrary to this view and stated that very little tetrachloroethylene is metabolized in man.

Ikeda and Ohtsuji (7), in experiments on the excretion of metabolites in rat urine, found 5.3 mg/kg body weight of trichloroacetic acid and 3.2 mg/kg body weight of trichloroethanol after exposing rats to 200 ppm tetrachloroethylene for 8 hours. Ikeda and Ohtsuji (7) found 4 - 20 mg/kg body weight of trichloroethanol and 4 - 35 mg/kg body weight of trichloroacetic acid in the urine of workers occupationally exposed to 20 - 70 ppm tetrachloroethylene. In workers exposed to 200 - 400 ppm tetrachloroethylene, 21 to 100 mg/L of trichloroethanol and 32 - 97 mg/L of trichloroacetic acid were found in the urine. In order to evaluate the effect of different routes of administration, Ikeda and Ohtsuji (7) injected rats with 2.78 mmol/kg body weight of tetrachloroethylene intraperitoneally. After collecting the urine for 48 hours, analysis showed the accumulation of 5.5 mg/kg body weight trichloroacetic acid and little or no trichloroethanol.

Ikeda et al. (8) found that urinary metabolite levels in man and rats increased until atmospheric concentrations of tetrachloroethylene reached 50 - 100 ppm; little increase was observed at higher concentrations. Results indicate that the capacity of human subjects to metabolize tetrachloroethylene is limited even at relatively low concentrations.

Experimenters have shown that the metabolites of tetrachloroethylene are very slowly excreted (10,12,14). Wolff (12) detected 1 ppm of tetrachloroethylene in the breath of humans 14 days after the subjects were exposed to a concentration of 100 ppm tetrachloroethylene (7 hours/day, 5 days). They found a respiratory half-life of 3 days for tetrachloroethylene. Ikeda and Imamura (10) reported a urinary half-life of 144 hours, and calculated a respiratory half-life of 65 hours (occupational exposure) from the data of Stewart et al. (11).

Lastly, tetrachloroethylene has been shown to accumulate in body tissues. Savolainen et al. (15) exposed rats to 200 ppm tetrachloroethylene for 6 hours per day for 4 days. Seventeen hours after the fourth day exposure, they found a marked accumulation of the solvent in the perirenal fat (622.2 nmol/g), as well as accumulations in the cerebrum (18.4 nmol/g) and cerebellum (13.1 nmol/g). After 6 hours additional exposure on the fifth day, 1724.8 nmol/g of tetrachloroethylene was found in the perirenal fat. Significant accumulations of tetrachloroethylene were also detected in the brain (cerebrum, 142.5 nmol/g; cerebelllum, 92.3 nmol/g) after 6 hours exposure on the fifth day.

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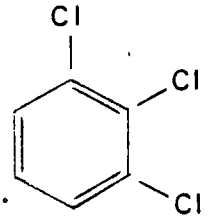
TRICHLOROBENZENE

$C_6H_3Cl_3$

Mol. Wt: 181.45 g/mole



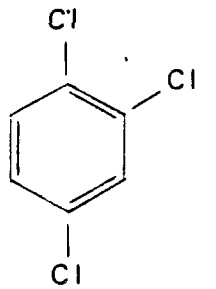
1,2,3-Trichlorobenzene

CAS: 000087616

SYN: vic-trichlorobenzene
1,2,6-trichlorobenzene

bp: 2180009 (at 760 mm Hg)

vp: .99 mm Hg (at 40°C)



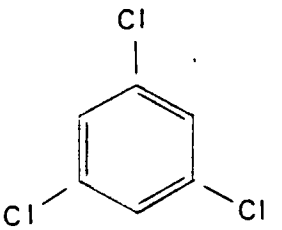
1,2,4-Trichlorobenzene

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)

Jondorf et al., in reports published in 1954 (1) and 1955 (2), identified the major urinary metabolites of the isomeric trichlorobenzenes in the rabbit as trichlorophenols, predominantly conjugated with glucuronic acid and ethereal sulfate. 1,2,3-Trichlorobenzene was found to generate 2,3,4-trichlorophenol as its major metabolite, with lesser quantities of 3,4,5-trichlorophenol and 3,4,5-trichlorocatechol. 1,2,4-Trichlorobenzene gave rise to 2,4,5- and 2,3,5-trichlorophenol, together with small amounts of 3,4,6-trichlorocatechol. 1,3,5-Trichlorobenzene, the least readily metabolized isomer, was found to generate only one phenolic metabolite, identified as 2,4,6-trichlorophenol. Trace amounts of mercapturic acids were detected from 1,2,3- and 1,2,4-trichlorobenzene and were identified by the same authors (2,3) as 3,4,5-trichlorophenylmercapturic acid, and 2,3,5- and 2,4,5-trichlorophenylmercapturic acids, respectively. Results and

a schematic representation of metabolites identified by Jondorf et al. (2), are presented in Table 1 and Figure 1.

Table 1 (2). Quantitative excretion of metabolites of the isomeric trichlorobenzenes.

Dose fed, 0·5 g./kg. wt. of rabbit. Figures refer to percentage of dose excreted during 5 days after dosing. Figures in parentheses are mean values. Superior figures indicate the number of experiments.

Trichlorobenzene fed	Percentage of dose excreted in the urine as: Glucuronide	Ethereal sulphate	Mercapturic acid	Total conjugation	Trichlorophenols: Free	Trichlorophenols: Total
1:2:3-	46–55 (50)[5]	9–13 (12)[3]	0·2–0·5 (0·3)[3]	55–69 (62)[3]	3–5 (4)[3]	64–89 (78)[4]
1:2:4-	18–33 (27)[3]	10–12 (11)[3]	0·2–0·5 (0·3)[3]	30–45 (38)[3]	1–2 (1·5)[3]	33–51 (42)[3]
1:3:5-	16–23 (20)[5]	1–5 (3)[5]	0 (0)[2]	17–28 (23)[5]	0·4–0·5 (0·5)[3]	7–13 (9)[5]

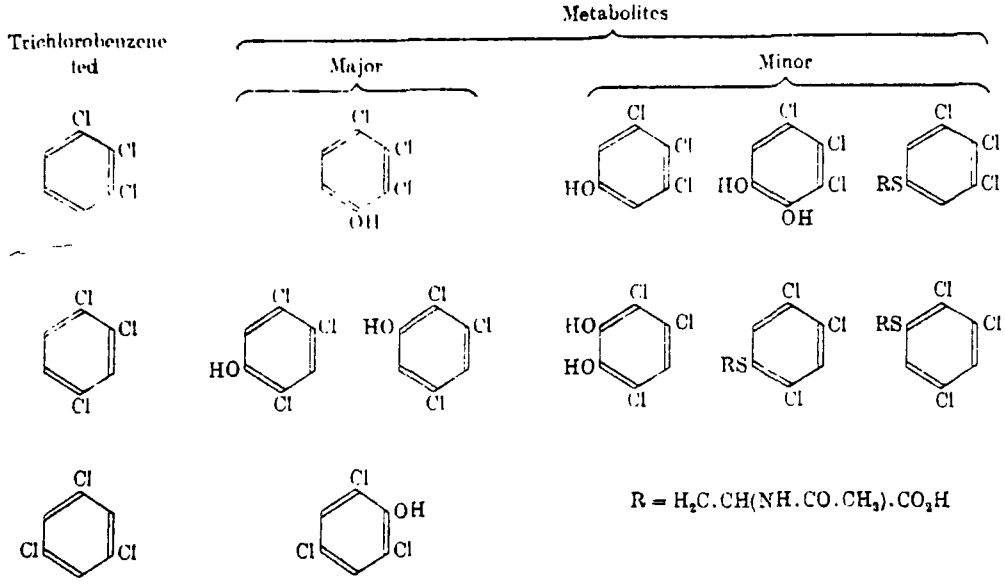


Fig. 1 (2). Orientation of the metabolites of trichlorobenzene.

Jondorf et al. (2) postulated the intermediacy of 3,4,5-trichloro-1,2-dihydro-1,2-dihydroxybenzene in the metabolism of the 1,2,3-trichlorobenzene, and 3,4,6-trichloro-1,2-dihydro-1,2-dihydroxybenzene as an intermediate of the 1,2,4-trichlorobenzene isomer. It was also proposed that 1,3,5-trichloro-2-hydro-1,2-dihydroxybenzene is an intermediate in metabolite production from 1,3,5-trichlorobenzene. These models are schematically represented in Figure 2 (2).

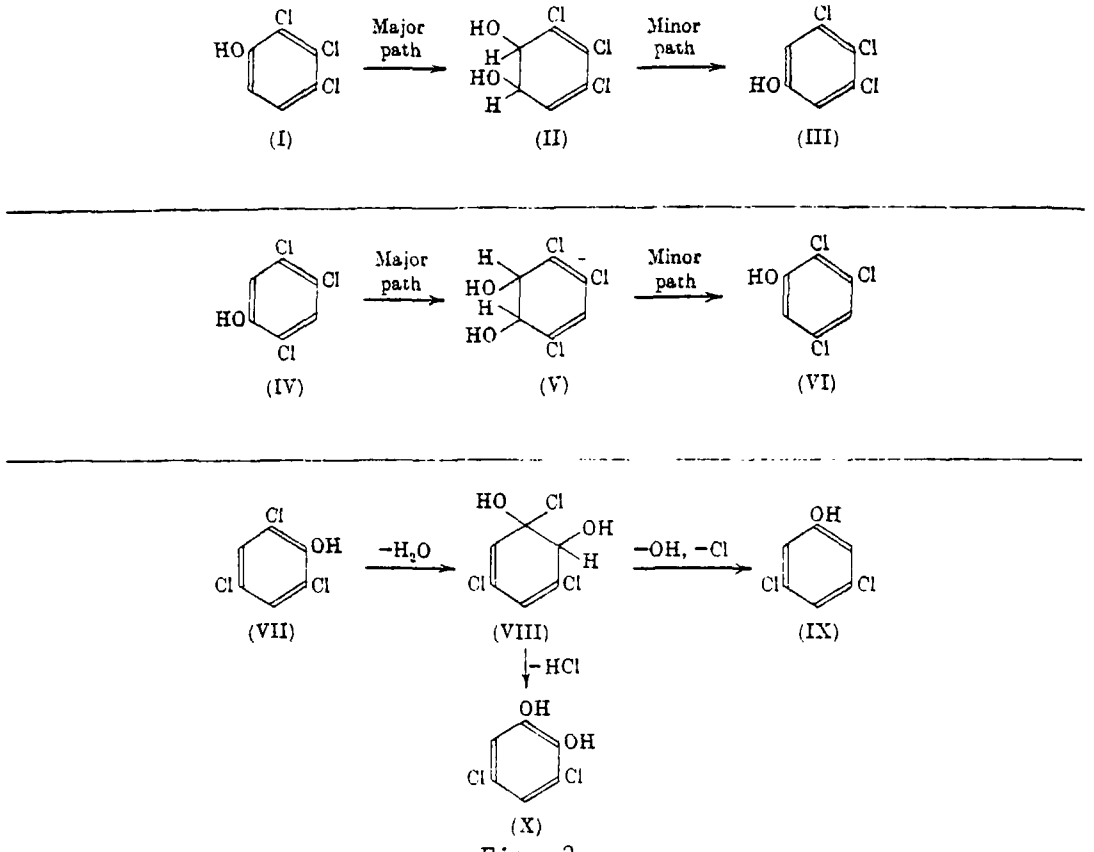


Fig. 2.

Fig. 2 (2). Proposed formation of trichlorinated 1,2-dihydro-1,2-dihydroxybenzene and 2-hydro-1,2-dihydroxybenzene intermediates in the metabolism of trichlorobenzene isomers

In a 1960 study, Parke and Williams (4) investigated the metabolism of 1,3,5-trichlorobenzene by rabbits and found that, in 9 days, approximately 10% of the dose administered (0.5 g/kg, oral) was excreted in the urine as 2,4,6- trichlorophenol. 4-Chlorophenol and 4-chlorocatechol were identified as minor urinary metabolites. The major portion of the administered dose was recovered unchanged; 19% was found in the gut contents, 13% in the feces, 32% in the body tissues, and 12% in expired air, 8 days afer dosing (4).

In 1976, Kolhi, et al. (5), reported a study of the metabolism of the isomeric trichlorobenzenes in the rabbit. Analysis was performed on urine and feces collected for 10 days following intraperitoneal administration of the trichlorobenzene isomers (300 mg/rabbit; ave. wt. 4-5 kg). Qualitative results were similar to those obtained in previous studies. However, evidence was provided for the presence, as metabolites, of 2,3,6- and 2,3,5-trichlorophenols from 1,2,3- and 1,3,5-trichlorobenzenes, respectively.

Kohli et al. (5), postulated the intermediacy of an arene oxide in phenolic metabolite production from the isomeric trichlorobenzenes. A schematic representation of trichlorobenzene metabolism, showing the arene oxide intermediates, is presented in Figure 3 (5).

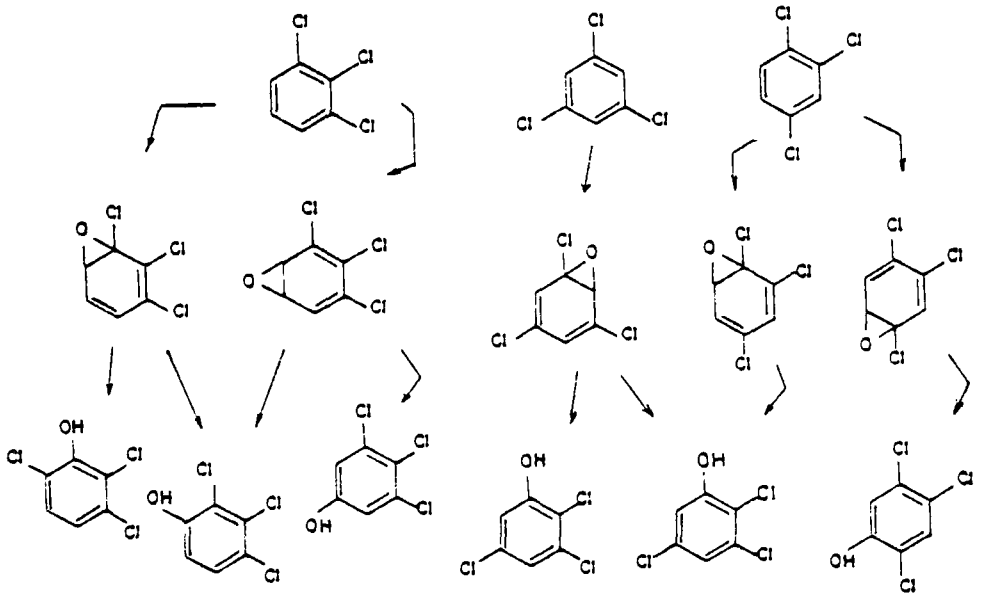


Fig. 3. Metabolism of isomeric trichlorobenzenes

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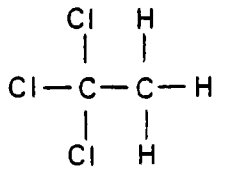
1,1,1-TRICHLOROETHANE

$C_2H_3Cl_3$



CAS: 000071556

Syn: methylchloroform; MC; alpha-trichloroethane

Mol wt: 133.41

bp: 74.1°C (at 760 mm Hg)

vp: 121.3 mm Hg (at 25°C)

The rapid and almost complete pulmonary excretion of 1,1,1-trichloroethane, or methylchloroform (MC) from the rat was demonstrated by Hake et al. (1). Young adult rats (170-183 gm) were injected intraperitoneally with 700 mg of 1,1,1-trichloroethane-1-C^{14} per kg. Urine, feces and expired air were collected for 25 hours, after which samples of blood, various organs (liver, intestines, spleen, kidneys, heart, lungs, and brain), retroperitoneal fat, skin, and muscle tissue were removed for carbon-14 assay. Radioactivity was measured with a liquid scintillation spectrometer and metabolites were identified by paper chromatography.

According to the data, 98.7% of the administered dose was excreted through the lungs as unchanged 1,1,1-trichloroethane-1-C^{14} and about 0.5% of the dose was excreted as $C^{14}O_2$. Much of the remaining radioactivity was detected in the urine as the glucuronide of 2,2,2-trichloroethanol-2-C^{14}, possibly formed by hydroxylation and conjugation of the parent compound. Very little carbon-14 activity was retained in the rat. Analysis of the organs and tissues showed no activity in the spleen, trace amounts in the liver, intestines, kidneys, heart, lung, brain, muscle, and hair, and less than 0.05% of the dose in the blood, fat, and feces each. The skin contained 0.08 - 0.12% of the dose of radioactivity, at least 90% of which was attributed to unchanged 1,1,1-trichloroethane-1-C^{14} (1).

Ikeda and Ohtsuji (2) studied the urinary metabolism of methylchloroform in the rat. Inhalation experiments were conducted in which Wistar-strain rats (70 g) were exposed to 200 ppm of MC in air for 8 hours. Urine was collected for 48 hours after the start of the exposure and analyzed colorimetrically by the Fujiwara reaction method to determine the amounts of trichloroethanol (TCE) and trichloroacetic acid (TCA). Very small amounts were detected: 3.1 and 0.5 mg/kg body weight of TCE and TCA, respectively. Similar results were obtained when rats were injected intraperitoneally with 2.78 mmol of MC per kg. Metabolite levels in urine after 48 hours represented the excretion of 3.5 mg TCE and 0.5 mg TCA/kg body weight. Metabolite excretion during the second 48-hour period amounted to an immeasurable amount of TCE and 0.3 mg TCA/kg. The authors noted that the detection of very low levels of urinary metabolites was consistent with the observation of Hake et al. (1), that 1,1,1-trichloroethane is almost entirely eliminated through the lungs while only a small amount is metabolized and excreted in urine.

Eben and Kimmerle (3) confirmed the findings of Hake et al. (1), and Ikeda and Ohtsuji (2) and furthermore reported that the amounts of urinary metabolites and MC (in expired air) were both time-dependent and dose-dependent. Acute and subchronic inhalation tests were conducted with male Wistar rats. In the acute exposure studies, rats were subjected to a single exposure of about 221 or 443 ppm of MC in air for 4 hours. Urine was collected daily for 3 or 4 days for gas-chromatographic analysis of TCE and TCA. Also, in several cases the concentration of MC in expired air was measured hourly up to 11 hours after exposure.

Results showed that in each case most of the total TCE in urine was excreted within 24 hours. The total amounts of TCE excreted from rats exposed to 221 ppm and 443 ppm MC were 126.2 ug and 206.5 ug, respectively, during the first day, and 7.5 and 8.6 ug, respectively, during the second day. The metabolite TCA was eliminated in much smaller quantities and at a more consistent rate, as follows: 3.2 ug (from the 221 ppm exposure) and 9.5 ug (443 ppm exposure) during the first day, and 8.1 and 10.6 ug, respectively, during the second day. The hourly measurements of MC in expired air indicated that MC content decreased exponentially with time. MC levels also varied with the dose administered. At the 221 ppm exposure level, expired air contained 2.488 mg MC in the 1st hour and only 0.050 mg MC in the 8th hour; at the 443 ppm exposure, the values were 5.719 mg and 0.098 mg MC during the 1st and 8th hours, respectively (3).

In the subchronic experiments, rats were exposed to 204 ppm MC for 8 hours per day, 5 days per week, for 14 weeks. Urinary excretion of TCE and TCA was measured after the daily exposure. Blood concentrations of MC and TCE were determined immediately after exposure, periodically throughout the 14 weeks. After 14 weeks, samples of the fat, brain, heart, liver, kidneys and spleen were analyzed for MC accumulation (3).

It was found that urinary TCA excretion was relatively constant during the entire experiment, ranging between 12 and 20 ug per consecutive 24-hour periods. Urinary TCE levels increased from about 93 ug in the first week to about 435 ug in the tenth, after which the levels decreased slightly.

Blood concentrations of MC and TCE were nearly constant; MC measured 0.677 to 1.000 ug/mL blood and TCE ranged form 0.059 to 0.88 ug/mL. The analyzed tissue samples showed no accumulation of MC.

Human inhalation exposure studies have shown results similar to the data obtained from experiments with rodents. The rapid pulmonary excretion of MC by humans was reported by Morgan et al. (4). The subjects were administered about 5 mg of ^{38}Cl methylchloroform in a single inhalation exposure and the expired air was analyzed for 1 hour by gamma-ray scintillation spectrometry. A total of 44% of the inhaled dose was excreted in the breath in one hour.

Astrand et al. (5), measured the concentration of methyl chloroform in alveolar air, arterial blood, and venous blood of 12 men in an inhalation study designed to simulate exposure to MC during light occupational work. Test variables included exposure to methylchloroform at 250 or 350 ppm in air, at rest or during light exercise (50, 100, or 150 W as measured on a bicycle ergometer), with or without 4% CO_2 added to inspiratory air to increase alveolar ventilation. Each exposure period was 30 minutes. Breath and blood samples were taken during and after exposure for gas chromatographic determination of MC content. The methylchloroform levels measured at the end of the exposure period are shown in Tables 1 and 2. In addition, results showed that MC levels in air and blood increased rapidly, usually leveling off after 20 to 30 minutes during exposure. After leveling off, there was no increase in MC concentration in air or arterial blood proportional to increased ventilation or circulation. The venous blood levels of MC rose at about the same rate as arterial blood levels. MC concentrations in expired air, venous blood, and arterial blood all dropped rapidly after exposure.

Table 1 (5). Arterial and venous blood concentrations at rest and exercise during exposure to 250 ppm and 350 ppm of methylchloroform. All data are derived from individual values at the end of each exposure period. Mean values and standard deviation are given except when n 3, the mean and extreme values are given.

	No. of subjects	Arterial blood conc. ppm	Venous blood conc. ppm	Arterio-venous difference ppm
250 ppm				
at rest	12	3.0 ± 0.2	1.4 ± 0.2	1.6 ± 0.2
50 watt	9	4.5 ± 0.2	3.1 ± 0.4	1.4 ± 0.3
100 watt	4	5.2 ± 0.2	3.5 ± 0.8	1.7 ± 0.8
150 watt	4	5.5 ± 0.3	4.4 ± 0.4	1.1 ± 0.3
350 ppm				
at rest	5	5.0 ± 0.5	3.0 ± 0.6	2.0 ± 0.4
			5.5	1.9
50 watt	5	7.2 ± 0.4	4.0 - 6.6	0.4 - 3.3
250 ppm				
		2.2	1.0	1.2
at rest	3	1.9 - 2.5	0.5 - 1.2	1.0 - 1.4
at rest +		3.3	1.2	2.2
4 % CO_2	3	3.0 - 3.9	0.9 - 1.3	1.7 - 2.6
50 watt +		3.9	1.9	2.0
4 % CO_2	3	3.2 - 4.5	1.4 - 2.3	0.9 - 2.6

Table 2. Alveolar air concentrations for 12 male subjects, at rest and during exercise, exposed to 250 ppm and 350 ppm of methylchloroform in air. V_A = alveolar ventilation per unit of time (dead space estimated at 150 cm^3 for all subjects).

	No. of subj.	V_A BTPS L/min	Alveolar conc. ppm
0 ppm			
at rest	8	8.9 ± 1.3*	-
250 ppm			
at rest	12	6.6 ± 0.4	125 ± 6
50 watt	9	22.5 ± 1.9	168 ± 7
100 watt	4	36.9 ± 2.4	210 ± 4
150 watt	4	59.5 ± 4.8	207 ± 14
350 ppm			
at rest	5	6.6 ± 0.7	179 ± 13
50 watt	5	21.8 ± 1.1	239 ± 17
250 ppm			
		6.3	128
at rest	3	5.1 - 7.0	110 - 139
at rest +		17.8	176
4 % CO_2	3	14.0 - 22.7	164 - 182
50 watt +		38.2	201
4 % CO_2	3	32.1 - 46.6	188 - 216

* measurement made after 5-10 min.

In another human exposure study, Stewart et al. (6), reported the methylchloroform concentrations in expired air and the levels of urinary metabolites TCE and TCA in 11 male subjects (31-62 yrs. old) exposed to 500 ppm methylchloroform in air for 6.5 - 7 hours per day for 5 days. The MC concentration in alveolar air decreased exponentially after the exposure period and was readily detected for a period of 10 days by infrared techniques. In some cases, methylchloroform was detected by gas chromatography as long as one month after exposure. A slight cumulative effect of MC concentration in alveolar air was observed corresponding to repeated exposures over the 5 day period. A leveling-off, or equilibrium, was reached between the 3rd and 4th days.

Results of the urinalyses are given in Table 3. The levels of TCE showed a progressive increase during the 5-day exposure period. TCE was still detected in urine 5 days after the final exposure but none was detected 12 days after exposure. TCA concentrations, however, did not increase much above the normal range (6).

Table 3 (6). Urinary excretion of TCA and TCE in five subjects during and following vapor exposure to methyl chloroform

	Methyl chloroform, 500 ppm seven hrs/day for five days	
Control value (mean and range)	TCA, mg/24 hr 14.2 (8.0 - 22.8)	TCE, mg/24 hr less than 1.0
1st exposure day	7.5 (2.6 - 10.5	20.1 (7.9 - 49.0)
2nd exposure day	10.9 (8.2 - 19.3)	30.1 (14.8 - 66.5)
3rd exposure day	12.3 (5.6 - 27.0)	29.3 (19.1 - 51.0)
4th exposure day	14.1 (7.8 - 19.2)	46.6 (23.4 - 93.6)
6th day following last exposure	18.0 (13.0 - 26.0)	7.0 (1.0 - 14.9)
12th day following last exposure	17.5 (8.0 - 22.0)	less than 1.0

A study of the long-term occupational exposure of men to MC in air was reported by Seki et al. (7). Concentrations of the urinary metabolites, TCE and TCA, and total trichloro-compounds (TTC) were measured in males (23-53 years old) who had been exposed to methylchloroform at 4, 25, or 53 ppm for 8 hrs/day, 5.5 days/week, for at least 5 years. Urinalyses were made daily for 1 week. The data, summarized in Table 4, indicated linear relationships between the concentration of MC in inhaled air and the levels of TTC, TCE, and TCA in urine. The biological half-life of methylchloroform, based on the decrease in urinary total trichlorocompounds, was calculated as about 8.7 hours.

Table 4 (7). Concentrations of metabolites in urine samples from workers exposed to methylchloroform at various concentrations for 8 hrs/day, 5.5 days/week, occupational exposure.

Conc. of MC in inhaled air (ppm)	No. of subjects	Metabolite concentrations* mg/L		
		TTC	TCE	TCA
4.3	10	2.0	1.2	0.6
24.6	26	8.2	5.5	2.4
53.4	10	13.9	9.9	3.6

* Values represent geometric means.

Although it has been established that almost all of an inhaled dose of methylchloroform is eliminated through the lungs and an additional portion of the dose is excreted as urinary metabolites, recent studies have shown that very small amounts of the parent compound, (methylchloroform) also accumulate in body tissues. The bioconcentration of methylchloroform in the perirenal fat, brain, liver, lung and blood of the rat was studied by Savolainen et al. (8). Adult male Sprague-Dawley rats were exposed to 20 umol/L (500 ppm) of MC in air for 6 hrs/day for 4 days. Gas-liquid chromatograph analyses were made on the 5th day, 17 hours after the last exposure period.

According to the results, methylchloroform accumulated primarily in the perirenal fat (16.9 nmol/g) while smaller amounts were detected in the organ tissues and blood (0.08 to 0.17 nmol/g). Additional exposure periods of 2,3,4, or 6 hours on day 5 increased the concentrations of MC in tissues and blood as shown (8):

	Methylchloroform concentration in tissues (nmol/g) after 4 days exposure (8)	
	17 hours after final exposure	immediately after 2-6 hours additional exposure on 5th day
Perirenal fat	16.9	183.5 - 276.0
Cerebrum	0.15	12.2 - 15.6
Cerebullum	0.17	13.2 - 21.3
Lungs	0.17	7.9 - 11.7
Liver	0.15	14.7 - 21.3
Blood	0.08	8.5 - 13.1

In a more extensive inhalation study, Holmberg et al. (9), reported the distribution of methylchloroform in the blood, liver, kidneys, and brain tissues of mice exposed to various air concentrations of MC for different periods of exposure. Male albino mice (NMRI strain, weighing 25 - 30 g) were subjected to concentrations of 10 ppm to 10,000 ppm of MC for 0.5 to 24 hours. Blood and organ tissues were analyzed by *gas chromatography*. In general, concentrations of methylchloroform were usually highest in the liver and lowest in the blood. After exposure to 100 ppm MC for 0.5 to 24 hours, the levels of MC ranged as follows: 3.5 to 14.0 ug MC per g of tissue (wet weight) in the liver, 3.0 to 8.1 ug/g in blood, 4.3 to 10.0 ug/g in the kidneys, and 4.4 to 9.2 ug/g in the brain tissues. Methylchloroform concentrations resulting from other exposure times and dose levels are given in Table 5.

Table 5 (9). Concentrations of methylchloroform in mouse tissues at different inspiratory air concentrations and exposure durations: means and standard deviations. Number of animals indicated in parentheses. Concentrations in ug of methylchloroform per gram of tissue (wet weight).

Exposure Time (h)	Blood	Liver	Kidney	Brain
10 ppm				
3	0.15 ± 0.07 (7)	0.43 ± 0.15 (10)	0.30 ± 0.14 (10)	0.21 ± 0.11 (10)
6	0.47 ± 0.20 (5)	1.2 ± 0.3 (5)	1.0 ± 0.2 (5)	0.6 ± 0.2 (5)
24	0.60 ± 0.16 (4)	1.5 ± 0.3 (5)	1.1 ± 0.2 (5)	0.8 ± 0.1 (5)
100 ppm				
0.5	3.0 ± 1.0 (9)	3.5 ± 1.3 (8)	4.3 ± 1.1 (9)	4.4 ± 1.3 (9)
1	4.8 ± 1.5 (8)	5.7 ± 2.5 (8)	7.7 ± 7.3 (8)	5.7 ± 1.4 (8)
2	4.2 ± 1.5 (8)	4.8 ± 2.3 (8)	4.7 ± 1.2 (8)	4.4 ± 1.3 (8)
3	4.5 ± 1.0 (9)	6.6 ± 1.2 (9)	5.3 ± 1.6 (8)	6.0 ± 0.9 (9)
4	8.1 ± 1.2 (8)	11.4 ± 2.0 (8)	10.0 ± 1.4 (8)	9.2 ± 0.9 (8)
4.5	5.6 ± 1.2 (8)	12.6 ± 2.2 (8)	6.0 ± 0.8 (7)	6.7 ± 0.9 (8)
5	6.2 ± 0.9 (8)	9.0 ± 4.5 (8)	8.0 ± 2.0 (8)	6.8 ± 1.7 (8)
6	6.0 ± 2.1 (9)	9.6 ± 2.1 (9)	8.6 ± 1.8 (9)	6.8 ± 0.9 (9)
16	5.8 ± 1.6 (4)	14.0 ± 6.8 (4)	8.3 ± 5.0 (4)	6.0 ± 0.7 (4)
24	6.3 ± 3.0 (9)	12.2 ± 4.6 (9)	5.9 ± 2.2 (9)	6.2 ± 1.3 (9)
1,000 ppm				
0.5	31 ± 24 (15)	63 ± 31 (14)	48 ± 13 (14)	36 ± 7 (14)
1	38 ± 6 (8)	68 ± 10 (8)	44 ± 9 (8)	43 ± 8 (8)
3	41 ± 22 (17)	114 ± 68 (17)	65 ± 29 (18)	53 ± 12 (18)
4.5	48 ± 5 (8)	118 ± 10 (8)	51 ± 7 (8)	59 ± 6 (8)
6	36 ± 16 (8)	107 ± 38 (10)	60 ± 16 (10)	57 ± 17 (9)
5,000 ppm				
0.5	103 ± 23 (8)	316 ± 16 (8)	189 ± 52 (8)	178 ± 18 (8)
1	144 ± 46 (8)	444 ± 118 (8)	256 ± 65 (8)	246 ± 54 (8)
3	165 ± 25 (8)	754 ± 226 (8)	153 ± 27 (8)	156 ± 24 (8)
10,000 ppm				
0.5	251 ± 93 (9)	824 ± 482 (8)	315 ± 71 (8)	361 ± 70 (8)
3	204 ± 31 (4)	1250 ± 409 (4)	498 ± 114 (5)	554 ± 76 (5)
6	404 ± 158 (3)	1429 ± 418 (5)	752 ± 251 (5)	739 ± 170 (5)

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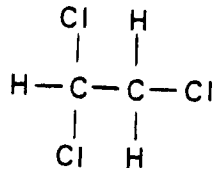
1,1,2-TRICHLOROETHANE

$C_2H_3Cl_3$



CAS: 000079005

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

Mol wt: 133.41 g/mole

bp: 113.77°C (at 760 mm Hg)

vp: 23.16 mm Hg (at 25°C)

A comprehensive investigation by Yllner et. al. (1), indicated that 1,1,2-trichloroethane is extensively metabolized, primarily through the formation of chloroacetic acid. Female albino mice were injected intraperitoneally with 0.1 to 0.2 g/kg doses of 1,1,2-trichloroethane-1,2-^{14}C (0.38 uCi/mg) and the elimination of radioactivity in urine, feces, and expired air was measured by liquid scintillation techniques for 3 days. Over 90% (range 82-98%) of the administered dose of radiation was eliminated in the first 24 hours, primarily in the urine. Total levels of carbon-14 activity eliminated in 3 days were reported as follows:

73-87% of the dose excreted in urine

0.1-2% detected in feces contaminated with urine

16-22% eliminated through the lungs

1-3% residual radioactivity found in whole-body homogenates taken at the end of the test period

Further analyses of the expired air by isotope dilution methods showed that about 3/5 of the radioactivity content was attributable to carbon dioxide and the remaining 2/5 to unchanged trichloroethane. The major urinary metabolites were determined by paper chromatography and isotope dilution analysis as shown:

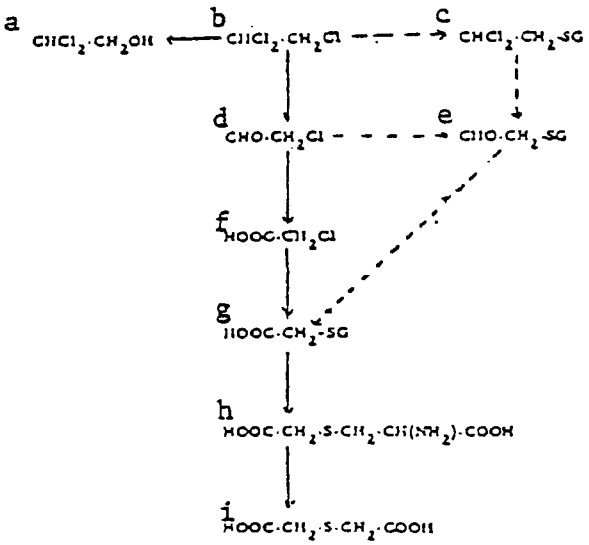
chloroacetic acid, 6-31% of urinary radioactivity

S-carboxymethylcysteine, 29-46% free and 3-10% conjugated

thiodiacetic acid, 38-42%

In addition, analysis revealed small quantities of glycollic acid, 2,2-dichloroethanol, oxalic acid, 2,2,2-trichloroethanol, and trichloroacetic acid. The close similarity of urinary metabolites obtained from 1,1,2-trichloroethane with those obtained from chloroacetic acid administered to mice in a previous experiment indicates that the metabolism of 1,1,2-trichloroethane occurs primarily via chloroacetic acid. Figure 1 represents the proposed metabolic pathway of 1,1,2-trichloroethane (1).

Ikeda and Ohtsuji (2) also reported the urinary excretion of very small quantities of trichloroacetic acid (TCA) and trichloroethanol (TCE) by rats exposed to 1,1,2-trichloroethane. In one inhalation experiment, male and female Wistar rats (70 g) were subjected to 200 ppm of 1,1,2-trichloroethane in air for 8 hours. Urine was collected for 48 hours from the beginning of the exposure, and determination of the metabolites by the Fujiwara color reaction indicated the excretion of 0.3 mg TCA/kg body weight and 0.3 mg TCE/kg. A second experiment in which rats were injected intraperitone- ally with 2.78 mmol of 1,1,2-trichloroethane per kg body weight resulted in the excretion of similar quantities of the metabolites; after the first 48 hours, metabolite excretion was determined to be 0.4 mg TCA/kg and 0.2 mg TCE/kg. Urine collected during an additional 48-hour period indicated excretion of another 0.3 mg TCA/kg and an immeasurable amount of TCE. The authors explained that the low levels of urinary metabolites may be attri- buted to the difficulty of the chemical transformation (the shifting of one Cl atom from one carbon atom to the other) required to form TCA or TCE from 1,1,2-trichloroethane. Also, it was noted that the estimates made by the Fujiwara reaction may include metabolites other than TCA and TCE.



a) 2,2-dichloroethanol
b) 1,1,2-trichloroethane
c) S-(2,2-dichloroethyl)-glutathione
d) chloroacetaldehyde
e) S-formylmethylglutathione
f) chloroacetic acid
g) S-carboxymethylglutathione
h) S-carboxymethylcysteine
i) thiodiacetic acid

The full arrows indicate the suggested routes and the dotted arrows the alternatives.

Fig. 1(1). Metabolic fate of 1,1,2-trichloroethane.

Morgan et. al. (3), conducted a human inhalation study which demonstrated that 1,1,2-trichloroethane has a low rate of pulmonary elimination. The subjects were administered about 5 mg of 38-Cl labelled 1,1,2-trichloro- ethane in a single inhaled breath and radioactivity in the expired air was measured by gamma-ray scintillation spectrometry for 1 hour after expo- sure. A total of 2.9% of the administered dose was excreted in the breath in 1 hour. The authors suggested an explanation for the low rate of 1,1,2- trichloroethane excretion as a function of the compound's partition coeffi- cients and diffusion rates. Measurements of partition coefficients for 1,1,2-trichloroethane between blood and air (44.2) and serum and air (37.1) at 40°C may indicate high solubility of the compound in blood lipids; however, high partition coefficients also represent slower diffusion across the alveolar membranes and consequently indicate a slower rate of 1,1,2-trichloroethane removed from the lungs during expiration.

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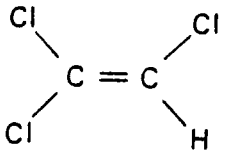
TRICHLOROETHYLENE

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/mole

bp: 87°C (at 760 mm Hg)

vp: 72.9 mm Hg (at 25°C)

The metabolism of trichloroethylene (TCE) was first reported in 1939. Since that time, much research has been conducted on the metabolism of TCE, especially in the field of human occupational exposure to TCE vapors. An excellent comprehensive review of the literature was published in 1977 by Waters et al. (1)

Trichloroethylene is rapidly taken up into the blood, especially through the lungs. After absorption, TCE quickly disappears from the blood at an exponential rate. A portion of the inhaled dose is expired unchanged in the breath, although most of the TCE is extensively metabolized and excreted in the urine. Small amounts of TCE metabolites may be eliminated in feces, sweat, and saliva. The TCE that is not eliminated quickly may be retained in the body, primarily in the fat tissues.

TCE is metabolized to two major metabolites: trichloroethanol and trichloroacetic acid (TCA). It is widely known that the alcohol is excreted mainly as a conjugate of glucuronic acid. A minor metabolite of TCE is monochloroacetic acid. An important intermediate metabolite is chloral hydrate, a very short-lived, transient compound which is readily oxidized to trichloroacetic acid. In general, the metabolic process includes rearrangement, oxidation, and reduction of TCE and its intermediates. Biotransformation occurs primarily in the liver and is NADPH dependent.

Absorption of TCE occurs rapidly, primarily via the lungs as a result of inhalation exposure. Maximal absorption of TCE occurs within the first few minutes of exposure, after which absorption decreases quickly until an air-to-blood TCE equilibrium is attained (1). The amount of TCE

absorbed by humans after exposure to various concentrations of TCE (54 to 390 ppm, for 160 minutes to 8 hours) ranges from 36% to 78% of the inspired TCE, with most reported values approaching 60% (2,3,4,5,6,7, 8,9). It has been demonstrated by Monster et al. (10), that the respiratory retention of TCE is proportional to the concentration in inspiratory air. The addition of work during exposure causes a further increase in the absorption of TCE (10,11).

After absorption, TCE is rapidly eliminated from the blood as shown in Figure 1, based on the human inhalation studies by Monster et al. (10). Subjects were exposed to 70 or 140 ppm TCE in air, with or without the addition of exercise (100 W on a bicycle ergometer), for 4 hours. It was found that the concentration of TCE in blood decreased greatly in the first few minutes after the exposure period, then declined at a much slower rate.

According to Fabre and Truhaut (1952, Br. J. Ind. Med., 9:39-43) as reported by Waters et al. (1), the transport of TCE (which is highly soluble in fat) in blood may be facilitated by the lipids in erythrocyte membranes. In inhalation experiments with rats exposed to 10 mg TCE/liter of air, 41.3 mg% TCE was detected in blood cellular components as compared to 2.5 mg% TCE found in blood plasma.

TCE is eliminated from the blood partly via pulmonary expiration. Daniel (12) determined that, after rats were given a single oral dose of 4.0, 7.5 or 8.6 uCi of ^{36}Cl-TCE, as much as 72-85% of the dose was exhaled as unchanged TCE. In humans, however, a relatively small amount, about 7-25%, of the TCE absorbed by inhalation is expired unchanged (2,6,7,10,11). Furthermore, Nomiyama and Nomiyama (13) reported that women expired less TCE than did men. In general, the expiration of TCE decreases exponentially (6,10,13,14,15). The rate constant for pulmonary elimination of TCE in humans has been calculated as k:0.14 hour^{-1} (6). Monster et al. (10), reported that trichloroethanol, in the expired breath of humans after exposure to TCE, also decreased exponentially. Ikeda (16) calculated the respiratory half-life of TCE to be about 25 hours, based on data from Stewart et al. (14), and Stewart et al. (1970, Arch. Environ. Hlth., 20:224).

Most of the TCE which has been absorbed into the body undergoes extensive metabolism and is eliminated in urine. Soucek and Vlachova (3) conducted a thorough study of the excretion of urinary TCE metabolites in humans. The subjects were exposed to known TCE concentrations (500-850 ug TCE per liter of air) for 5 hours. Urine was collected continuously during the exposure period and for 3 days after exposure, and subsequent samples were taken daily for analysis until metabolites could no longer be detected. The primary metabolite, trichloroethanol, accounted for a total of about 50% of the absorbed TCE. Trichloroethanol appeared in the urine soon after the start of the exposure and its concentration increased rapidly until a maximum level was reached a few hours after the end of the exposure period. The level of trichloroethanol in urine then decreased at two successive exponential rates: initially the concentration dropped at a fast rate for 3-4 days and then decreased at a slower rate for 7-9 days. Trichloroethanol was excreted for an average of 350 hours. The second major urinary metabolite, trichloroacetic acid (TCA), was detected

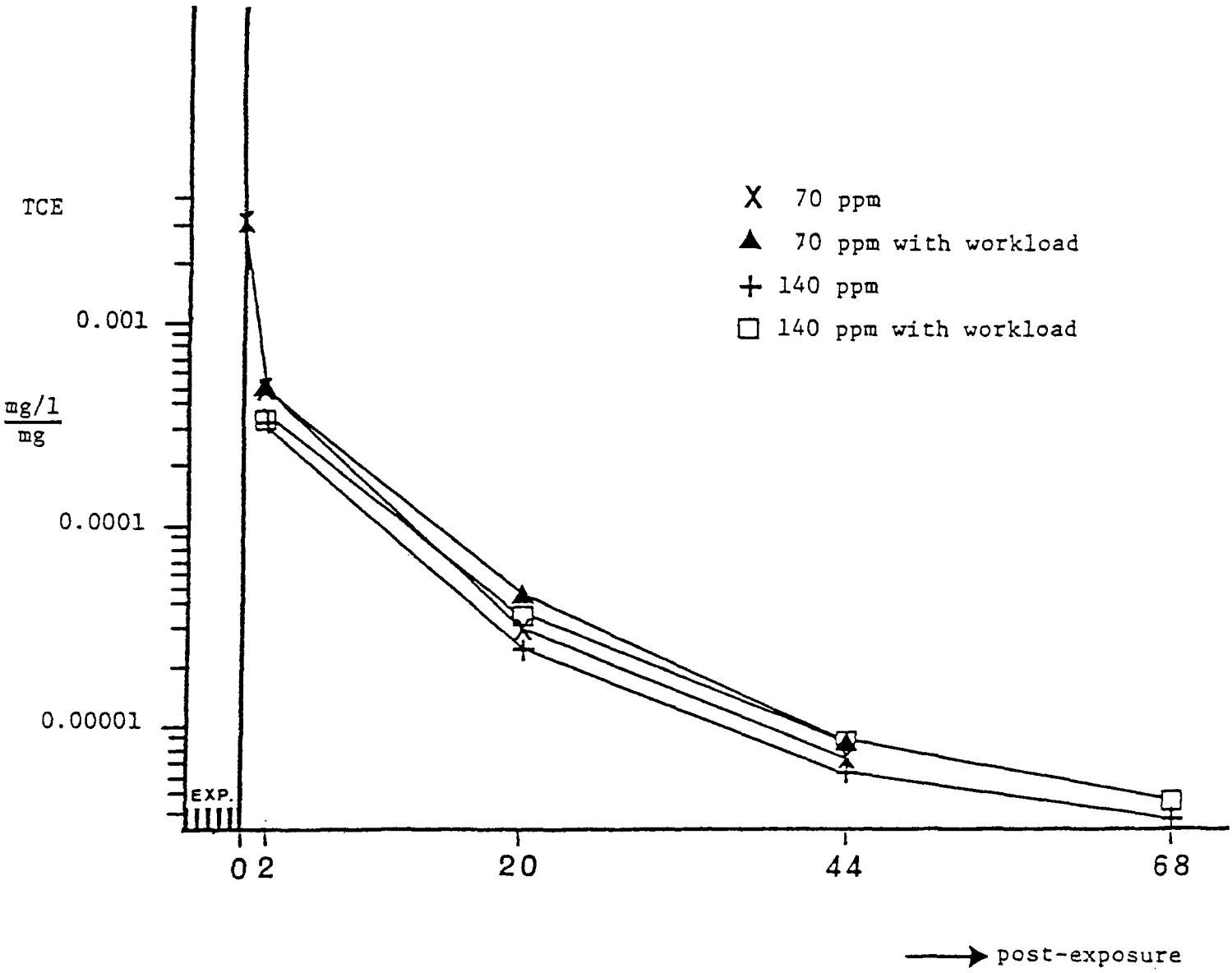


Figure 1. Trichloroethylene concentrations in human blood (as fraction of dose/liter whole blood) after 4 hours inhalation exposure to 70 or 140 ppm TCE, at rest or with work (two ½-hour periods of exercise, 100 W, on a bicycle ergometer during exposure). Data points were calculated by dividing individual concentrations (mg/l) by individual dose (mg). The figure represents the means of four subjects under each exposure condition. Redrawn from Monster et al. (10).

in amounts equal to about 19% of the TCE dose. TCA in urine was found immediately after the beginning of TCE inhalation. The concentration of TCA then increased slowly, peaked at 24-48 hours, and decreased exponentially in two phases. The average total excretion time for TCA was 387 hours. In addition, a diurnal variation was observed in the amount of TCA excreted; a daily maximum level of TCA occurred at 1:00 p.m. each day. Excretion of a third urinary metabolite, monochloroacetic acid (MCA), accounted for 4% of the inhaled TCE. Starting a few minutes after the beginning of TCE inhalation, the MCA concentration increased rapidly, reached a maximum level at the end of the exposure, and then declined at an exponential rate. The period of MCA excretion was about 112 hours. Altogether, a total of 73% of the TCE absorbed by inhalation was excreted in urine in the form of monochloroacetic acid, trichloroacetic acid, and trichloroethanol, in a ratio of 1:5:12 by quantity.

Similar results were obtained from human inhalation studies by Bartonicek (8) in which 8 subjects were exposed to 1,042 ug of TCE per liter of air for 5 hours. Urine was analyzed daily for 3 weeks. The author reported that an average of 45.4% of the inhaled TCE was excreted as trichloroethanol and 31.9% as trichloroacetic acid. The value for the ratio of TCA/trichloroethanol excretion was about 1.44, compared to the ratio of 2.4 found by Soucek and Vlachova (3). Other researchers have determined TCA/trichloroethanol ratios of 1.99 and 1.84, as cited by Bartonicek (8).

Several authors have also reported experimental data comparable to Bartonicek (8) and Soucek and Vlachova (3) demonstrating that humans excrete nearly twice as much trichloroethanol (32.7-68.8% of absorbed TCE) as trichloroacetic acid (17.7-43.9%) after inhalation of various concentrations of TCE (54-390 ppm) for up to 8 hours (2,6,17,18).

It has been well established from the literature that trichloroacetic acid is excreted in urine at a much slower rate and for a longer time than trichloroethanol, and that the total amount of trichloroethanol excreted is greater than the amount of TCA. A similar time course of trichloroethanol and TCA urinary elimination has been reported from long-term studies of repeated inhalation exposures or occupational exposure of humans to trichloroethylene (15,17,19,20). An example of the elimination pattern, similar to that described by Bartonicek (8), is shown in Figure 2 (15). Muller and Spassowski (19) described the pattern of elimination in terms of a reverse ration by determining that the trichloroethanol-to-TCA ratio decreases from 10 to 1-2, over day 1 to day 5
of the exposure.

Researchers have concluded that the concentrations of trichloroethanol and trichloroacetic acid in human urine are proportional to the environmental concentration of TCE, based on the results of occupational exposure studies (16,17,21) . Ikeda (16) and Ikeda et al. (21), reported a linear correlation between TCE in air and metabolite levels in urine. Examples of the relationship are given in Table 1. It was noted that the urinary concentration of TCA deviated from the linear regression line when the TCE concentration in air exceeded 50 ppm (16,21). Ikeda (16) also used the data from occupational exposure studies to calculate a mean urinary half-life of 41 hours for TCE in humans.

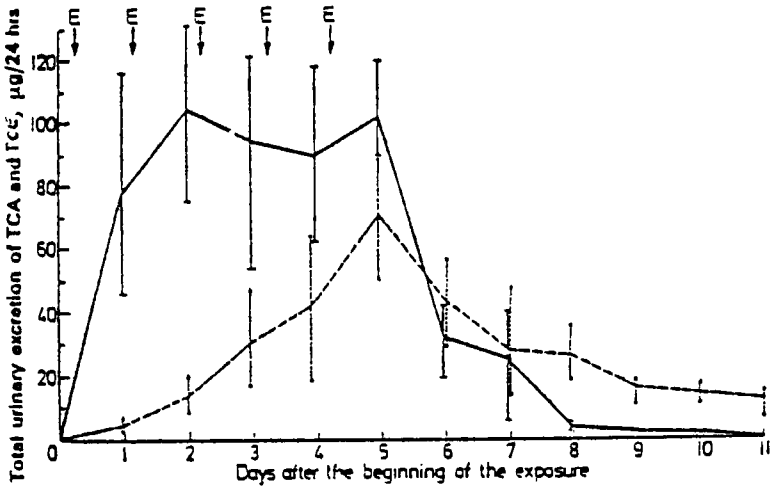


Fig 2. Urinary trichloroethanol (TCE) and trichloroacetic acid (TCA)-excretion (24-h specimens) during and after repeated exposure (on 5 successive days, 4 h/day) to a TCE concentration of 48.0 ± 3 ppm (mean of 4 subjects). ————TCE.
--------TCA. (From Ref. 15).

Other species have been shown to metabolize TCE to the same major metabolites (TCA and trichloroethanol) found in humans. The amounts of metabolites excreted vary widely among species. A comprehensive review of the literature regarding TCE metabolism in experimental animals was published in 1970 by the Joint FAO/WHO Expert Committee on Food Additives (22). Dogs reportedly excreted 5-8% of retained TCE as TCA and 15-20% as trichloroethanol for up to 4 days following exposure. After inhalation of TCE, rats excreted 4% of the dose as TCA. The lungs and spleen were probably the major metabolic sites. Following oral administration of TCE, rats excreted 3% as TCA and 15% as trichloroethanol. In another

Table 1(21). Metabolite concentrations in urine samples from workers exposed trichloroethylene at various concentrations for 8 hrs/day, 6 days/week.

Trichloroethylene (ppm)	No. of Workers	TTC[a]	Metabolite concentration (mg/liter)	
			Trichloroethanol	TCA
10	6	60.5	42.0	17.6
25	4	164.3	77.3	77.2
50	5	418.9	267.3	146.6
60	5	468.0	307.9	155.4
120	4	915.3	681.8	230.1

[a]TTC represents total trichloro-compounds.

case, rats were given ^{36}Cl-TCE by gavage and of the 15% excreted in urine, 1-5% was detected as TCA and 10-15% as trichloroethanol (12,22). Rabbits and guinea pigs showed the presence of TCA in urine after TCE exposure (22). In experiments with calves fed 3 or 12 g of TCE daily for 4 or 5 days, urinalyses showed the excretion of about 1% as TCA, 13-25% as trichloroethanol, and traces of TCE (22,23).

Although it has been shown in the literature that almost all of the TCE which is absorbed into the human body is eventually eliminated in the urine or expired air, Bartonicek (8) reported that small amounts of TCE metabolites may also be excreted in feces, sweat, and saliva. Samples of each were collected and analyzed on the third day after human subjects had been exposed to 1,042 ug TCE/liter of air for 5 hours. From the results it was determined that 8.4% of the TCE dose was present as both metabolites in the feces; sweat contained 0.15-0.35 mg TCA/100 ml and 0.10-1.92 mg trichloroethanol/100 ml; and saliva contained 0.10-0.15 mg TCA/100 ml and 0.09-0.32 mg trichloroethanol/100 ml. The author stated that despite the fact that the metabolite levels were very low in feces, sweat, and saliva, the data may be significant in partially explaining the fate of trichloroethylene that is absorbed but not accounted for in urine or expired air.

Several studies have been reported regarding blood levels of trichloroethylene metabolites (8,15,20,24). In one such study, Muller et al. (24) reported maximum levels of 50 ug TCA/ml of blood and 2.3 ug trichloroethanol (non-glucuronic fraction) per ml of blood when human subjects were exposed to 50 ppm TCE for 6 hours per day for 5 days. The significant accumulations of TCA may be attributed to a high plasma protein binding rate (90-86% for 10-50 ug TCA/ml). The authors also noted that the pattern of elimination of TCA and trichloroethanol from the blood parallels the course of urinary elimination of TCE metabolites. Muller et al. (24) also determined the half-lives of TCA and trichloroethanol in blood at 100 hours and 12 hours, respectively. Levels of TCA persisted in blood for over two weeks after exposure to TCE (24).

In the results of similar sub-acute inhalation experiments, Kimmerle and Eben (15) reported concentrations of trichloroethanol in human blood higher than the levels reported by Muller et al. (24). Data obtained from humans exposed to 48 ppm of TCE for 4 hours per day for 5 days are summarized in Table 2 (15).

Table 2 (15). Concentrations of trichloroethanol in the blood of 8 humans exposed to 48 ppm of TCE for 4 hours/day, for 5 days. Figures represent ranges of the maximum concentrations found on each day. Concentrations are expressed in ug/mL.

Days of exposure	Trichloroethanol concentration(12:00 noon)	Days after exposure	Trichloroethanol concentration(8:00 a.m.)
1	1.275 - 2.849	1	0.510 - 2.110
2	0.567 - 1.296	2	0.179 - 0.507
3	2.010 - 2.530	3	n.d.* - 0.272
4	1.565 - 2.580	7	0 - 0.030
5	1.974 - 2.870		

Kimmerle and Eben (15) also conducted an acute exposure experiment in which human subjects were exposed to 40 or 44 ppm of TCE for 4 hours. The blood levels of trichloroethanol at the end of the inhalation ranged from 0.706 to 1.776 ug/ml blood. At 96 hours after the start of exposure, less than 0.123 ug/ml was detected.

Ertle et al. (20), reported data comparable to Muller et al. (24), and Kimmerle and Eben (15). Humans were exposed to 50 ppm constant, 250 ppm (for 12 min./hr.), or 100 ppm constant TCE concentrations for 6 hours per day for 5 days. Results showed a day-to-day accumulation of trichloroethanol in the blood. Maximum trichloroethanol concentrations attained for each of the three exposure levels were 2.0, 2.5, and 5.0 ug/ml, respectively.

Bartonicek (8) measured the concentration of TCA in separate fractions of plasma and red blood cells of humans (exposed to 1043 ug TCE/L air, 5 hrs). The mean values, obtained on the third day after exposure, were reported as follows: plasma, 2.4 mg/100 ml plasma; red blood cells, 0.5 mg/100 ml red cell mass.

TCE that is absorbed but not metabolized (and excreted) immediately may be retained in adipose tissues (1). According to Fabre and Truhaut (1952, Br. J. Ind. Med. 9:39-43) as reported by Waters et al. (1), analysis of various tissues of the guinea pig following inhalation exposure to TCE revealed that TCE and TCA accumulated in most tissues, but concentrations were consistently highest in the fat tissue. Following chronic inhalation of 6-9 mg TCE/liter of air (4-5 hrs/day, 5-23 days), the concentration of trichloroethylene in fat was found to be 3.1 - 3.9 mg/100 g fresh tissue, and the concentrations of trichloroacetic acid in fat ranged up to 4.4 mg/100 g tissue. Levels of TCA were higher than TCE in all tissues.

A comprehensive scheme for the metabolism of TCE, based on a review of the literature, was proposed by Waters et al. (1), as shown in Figure 2. The first step in TCE metabolism is the formation of chloral hydrate via trichlorethylene oxide or trichlorethylene glycol (1). Spectral evidence for the formation of the TCE epoxide has been demonstrated in vitro by Uehleke et al. (25). The oxide intermediate is very unstable, rearranging spontaneously to trichloroacetalolehkyde and subsequently to chloral hydrate (1). In general, the intramolecular rearrangement of TCE to chloral hydrate involves chlorine migration and is mediated by a microsomal NADPH/O_2 - dependent reaction occuring primarily in the liver (1).

Chloral hydrate formation was reported in vitro (26,27) and in human blood plasma (28). According to the Waters et al. (1), review, chloral hydrate is also a short-lived intermediate, having a biological half-life of less than 30 minutes in humans, 10 minutes in dogs, and 10-20 minutes in mice. The compound is rapidly metabolized, undergoing either, a) oxidation to trichloroacetic acid by the action of chloral hydrate dehydrogenase (NAD coenzyme) or b) reduction to trichloroethanol by liver alcohol dehydrogenase (NADH coenzyme). Trichloroethanol is usually excreted in urine as a conjugate of glucuronic acid; conjugation takes place primarily in the liver (1). As described earlier, Soucek and Vlachova (3) determined the presence of small amounts of monochloroacetic acid as another final metabolite of trichloroethylene.

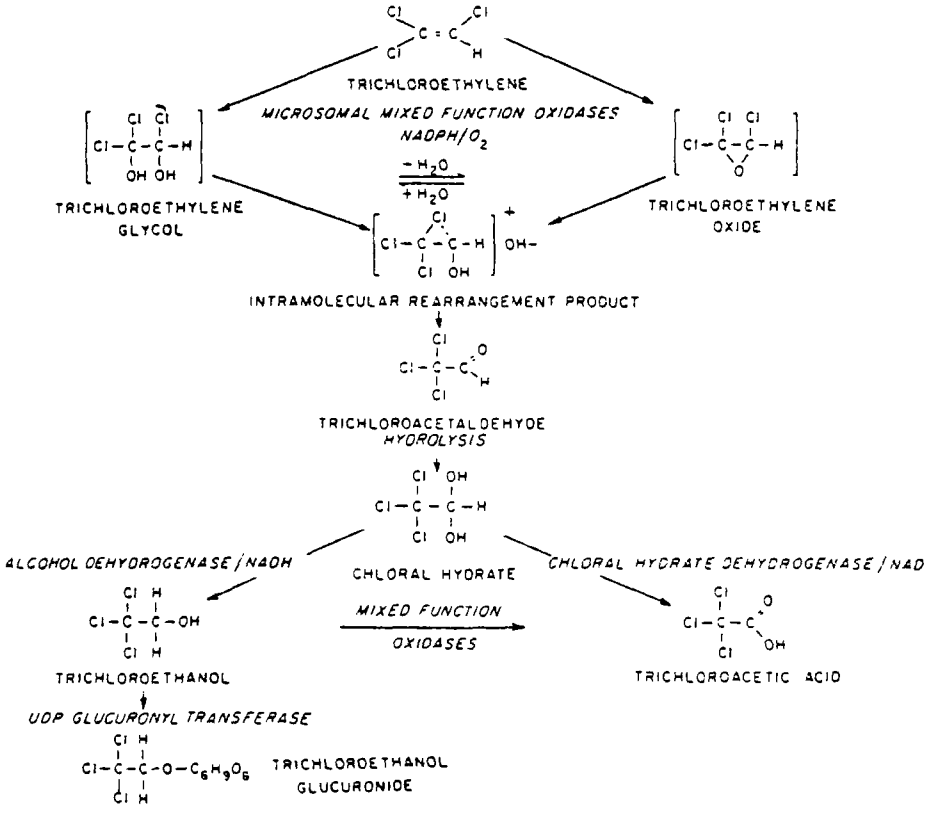


Figure 3. Proposed intermediary metabolism of TCE (1)

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APPENDIX A

Summary Table

of

Experimental Data

INTRODUCTION

The following table summarizes the experimental data reported in the literature on the 30 halogenated hydrocarbon compounds discussed in the preceding section. Although the table was intended to accompany the metabolism chapters, a bibliography (pages 300-309) has been included in order that the table may be used as a separate indexed reference.

The information under each compound is listed, by corresponding author(s), in the same order as it was discussed in the metabolism chapters. Included are the experimental species and the rate (or dose) and methods of administration, followed by the name of the metabolite its observed concentration expressed as a percentage of the administered dose of the parent compound (unless otherwise indicated), the medium (urine, expired air, blood, feces, or tissues) in which the metabolite was measured, and the reference. Additional data and details of the experimental method may be obtained from the original reference.

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Benzyl Bromide	rabbit	0.2 g/kg, by stomach tube	mercapturic acid	19%	urine	A-1
			ethereal sulfate	2%	urine	A-1
Benzyl Chloride	rabbit	0.2 g/kg, by stomach tube	mercapturic acid	49% (37-67) (24 hrs)	urine	B-1
			glycine conjugate (benzoic or phenyl-acetic)	20% (12-16) (24 hrs)	urine	
			glucosiduronic acid (mainly phenols)	0.4% (0-5) (24 hrs)	urine	
			unconjugated acids (benzoic or phenylacetic)	17% (24 hrs)	urine	
	guinea pig	unspecified	mercapturic acid	4%	urine	B-2
	rat	unspecified	mercapturic acid	27%	urine	
Bromobenzene	rabbit	0.5 g/kg, oral dose	bromobenzene (unchanged)	6% (1-2 days)	expired air	C-1
	rabbit	0.5 g/kg, stomach tube	bromobenzene (unchanged)	6.3%	expired air	C-2
	rabbit	210 mg/kg, via stomach tube	total conjugates	97.9%	urine	C-3
			glucuronide	40.2%	urine	
			ethereal sulfate	36.8%	urine	
			mercapturic acid	20.9%	urine	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Bromobenzene (continued)	rabbit	0.5 g/kg, oral dose	total O-conjugates	58% (1-2 days)	urine	C-1
			mercapturic acid	25% (1-2 days)	urine	
			monophenols	2-3% (1-2 days)	urine	
			catechols	28% (1-2 days)	urine	
	rabbit	0.5 mg/kg, via stomach tube	4-bromocatechol	28.2% (4 days)	urine	C-4
			bromophenylmercapturic acid	22%	urine	
(a) figure shown is percent yield of metabolite obtained by extraction and purification of the ether extracts of hydrolyzed rabbit urine.	rabbit	50 mg/kg, i.p. injection	4-bromophenol	1.2%(a) (10 days)	urine	C-5
			3-bromophenol	1.0%(a) (10 days)	urine	
	rat	10.0 mmol/kg, i.p. injection	bromophenylmercapturic acid	48% (48 hrs)	urine	C-6
			4-bromophenol	37% (48 hrs)	urine	
			bromocatechol	6% (48 hrs)	urine	
			bromophenyldihydrodiol	4% (48 hrs)	urine	
			2-bromophenol	3% (48 hrs)	urine	
	rat	0.05 mmol/kg, i.v. injection	bromophenylmercapturic acid	70% (48 hrs)	urine	C-6

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Bromobenzene (continued)	rat	0.05 mmol/kg, i.v. injection	4-bromophenol	18% (48 hrs)	urine	C-6
			bromocatechol	4% (48 hrs)	urine	
			bromophenyldihydrodiol	4% (48 hrs)	urine	
			2-bromophenol	3% (48 hrs)	urine	
	rat	dosage not stated; i.p. injection	4-bromophenol	40% (48 hrs)	urine	C-7
			2-bromophenol	4% (48 hrs)	urine	
			3,4-bromocatechol	4% (48 hrs)	urine	
			2,3-bromocatechol	trace (48 hrs)	urine	
			3,4-bromophenyldi-hydradiol	3% (48 hrs)	urine	
			2,3-bromophenyldi-hydrodiol	trace (48 hrs)	urine	
	rat	288 umol ^{14}C-bromobenzene	total urinary metabolites	23 umol (4 hrs)	urine	C-8
				63 umol (8 hrs)		
				240 umol (24 hrs)		
			mercapturic acids	15.1 umol (4 hrs)	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Bromobenzene (continued)	rat	288 umol ^{14}C-bromobenzene	mercapturic acids	41.2 umol (8 hrs)	urine	C-8
				141.6 umol (24 hrs)		
			phenolic metabolites	5.5 umol (4 hrs)	urine	
				15.1 umol (8 hrs)		
				64.7 umol (24 hrs)		
	rat	20 mg/kg ^{14}C-bromobenzene, i.v. injection	bromobenzene metabolites (unspecified)	11% (initial 30 min.)	bile	C-9
				18% (2nd 30 min.)	bile	
				56% (3 hrs, cumulative)	bile	
				80% (3 hrs, cumulative)	bile plus urine	
	rat	750 mg/kg, i.p. injection	bromobenzene	5,600 ug/g (4 hrs)	adipose tissue	C-8
				400 ug/g (24 hrs)		
				132 ug/g (4 hrs)	stomach	
				16.8 ug/g		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Bromobenzene (continued)	rat	750 mg/kg, i.p. injection	bromobenzene	235 ug/g (4 hrs)	kidney	C-8
				18.9 ug/g (24 hrs)		
				282 ug/g (4 hrs)	liver	
				10.7 ug/g (24 hrs)		
				206 ug/g (4 hrs)	brain	
				7.0 ug/g (4 hrs)		
				146 ug/g (4 hrs)	heart	
				5.0 ug/g (24 hrs)		
				142 ug/g (4 hrs)	lung	
				6.2 ug/g (24 hrs)		
				34 ug/g (4 hrs)	plasma	
				2.1 ug/g (24 hrs)		
Bromoform	rat liver microsomal fractions	60 umol bromoform added to incubation mixture; incubated at 37°C for 15 min.	carbon monoxide	100%	in vitro	D-1

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
3-Bromopropylbenzene	rabbit	0.25 g/kg, by stomach tube	ethereal sulphate	20%	urine	E-1
			ether soluble acid (primarily glucosid-uronic acid; also mercapturic acid and glycine conjugates)	69%	urine	
			N-acetyl-S-(3-phenyl-propyl)-L-cysteine	unspecified amount	unhydrolysed urine (acidic)	
			phenaceturic acid	unspecified amount	unhydrolysed urine (acidic)	
			phenolic metabolites (unspecified)	unspecified amount	hydrolysed urine (conjugated phenolic)	
Carbon tetrachloride	human	80 ppm ^{14}carbon tetrachloride, via single breath inhalation	^{14}carbon tetrachloride (unchanged)	33% (1 hr)	expired breath	F-1
	monkey	46 ppm ^{14}carbon tetrachloride, inhalation for 344 minutes	^{14}carbon tetrachloride (unchanged)	40% (1800 hrs)	expired breath	F-2
	rat	1.0 mL ^{14}carbon tetrachloride/kg, intraduodenal	^{14}carbon tetrachloride (unchanged)	85% (18 hrs)	expired breath	F-3
	rabbit	1 ml/kg, via stomach tube	carbon tetrachloride (unchanged)	787 ug/g (6 hrs)	fat tissue	F-4
				96 ug/g (24 hrs)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Carbon tetrachloride (continued)	rabbit	1 ml/kg, via stomach tube	carbon tetrachloride, unchanged	45 ug/g (48 hrs)	fat tissue	F-4
				96 ug/g (6 hrs)	liver	
				7.7 ug/g (24 hrs)		
				3.8 ug/g (48 hrs)		
	sheep	0.12 ml/kg, directly to rumen	carbon tetrachloride	398 ug, total (6 hrs)	bile	F-5
				433 ug, total (day 1)		
				7 ug, total (day 2)		
				trace-6 ug, total per day (day 3-7)		
	sheep	0.15 ml/kg, directly to rumen	carbon tetrachloride	438 ug, total (6 hrs)	bile	F-5
				543 ug, total (day 1)		
				9 ug, total (day 2)		
				nil-8 ug, total per day (day 3-7)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Carbon tetrachloride (continued)	rabbit	1.0 ml/kg via stomach tube	carbon tetrachloride (unchanged)	37 ug/g (6 hrs)	bile	F-5
				7.8 ug/g (24 hrs)		
				1.1 ug/g (48 hrs)		
	sheep	0.1 mg/kg, directly to rumen	carbon tetrachloride	19.2 ug, total (day 1)	urine	F-5
				5.9 ug, total (day 2)		
				4.6 ug, total (day 3)		
				trace-1.3 ug, total per day (day 4-7)		
	sheep	0.12 ml/kg, directly to rumen	carbon tetrachloride	1.2 ug, total (day 1)	urine	F-5
				1.0 ug, total (day 2)		
				0.7 ug, total (day 3)		
				trace-0.7 ug, total per day (day 4-7)		
	rabbit	110 ppm, inhalation (4 hrs)	carbon tetrachloride	trace (at end of exposure)	blood	F-6

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Carbon tetrachloride (continued)	rabbit	225 ppm, inhalation (4 hrs)	carbon tetrachloride	0.2 mg/100 mL blood (at end of exposure)	blood	F-6
		345 ppm, inhalation (4 hrs)	carbon tetrachloride	0.6 mg/100 mL blood (at end of exposure)	blood	F-6
		600 ppm, inhalation (4 hrs)	carbon tetrachloride	0.4 mg/100 mL blood	blood	F-6
	rat	0.1-0.5 ml, via stomach tube	chloroform	0.037 mg/g (15 min.)	liver	F-7
				0.027 mg/g (30 min.)		
				0.007 mg/g (240 min.)		
	rabbit	1 ml/kg, via stomach tube	chloroform	4.7 ug/g (6 hrs)	fat tissue	F-4
				1.0 ug/g (24 hrs)		
				0.4 ug/g (48 hrs)		
				4.9 ug/g (6 hrs)	liver	
				1.0 ug/g (24 hrs)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Carbon tetrachloride (continued)	rabbit	1.0 ml/kg, via stomach tube	chloroform	0.8 ug/g (48 hrs)	liver	F-4
	rabbit	1.0 mL/kg, via stomach tube	chloroform	0.50 ug/g (6 hrs)	bile	F-5
				0.14 ug/g (24 hrs)		
				0.45 ug/g (48 hrs)		
	sheep	0.1 ml/kg, directly to rumen	chloroform	3.7 ug/, total (day 1)	urine	F-5
				2.0 ug, total (day 2)		
				1.8 ug, total (day 3)		
				trace-0.8 ug total per day (day 4-7)		
	sheep	0.12 ml/kg, directly to rumen	chloroform	6.6 ug, total (day 1)	urine	F-5
				3.3 ug, total (day 2)		
				2.2 ug, total (day 3)		
				trace-2.0 ug, total per day (day 4-7)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Carbon tetrachloride (continued)	sheep	0.12ml/kg, directly to rumen	chloroform	0 ug, total (6 hrs) 241 ug, total (day 1) 122 ug, total (day 2) 0-95 ug, total per day (day 3-7)	bile	F-5
	sheep	0.15 ml/kg, directly to rumen	chloroform	0 ug, total (6 hrs) 210 ug, total (day 1) 126 ug, total (day 2) nil-120 ug, total per day (day 3-7)	bile	F-5
	dog	5 ml/hr, inhalation (3 hrs)	chloroform	0.1-0.5 mg, total (2 hrs)	expired air	F-8
	rat	1.0 ml ^{14}carbon tetrachloride/kg, intraduodenal	^{14}carbon dioxide	1% (18 hrs)	expired breath	
	monkey	46 ppm ^{14}carbon tetrachloride, inhalation for 344 minutes	^{14}carbon dioxide	11% (1800 hrs)	expired breath	F-2

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Carbon tetrachloride (continued)	rabbit	1 ml/kg, via stomach tube	hexachloroethane	4.1 ng/g (6 hrs)	fat	F-4
				16.5 ng/g (24 hrs)		
				6.8 ng/g (48 hrs)		
				1.6 ng/g (6 hrs)	liver	
				4.2 ng/g (24 hrs)		
				1.0 ng/g (48 hrs)		
	rat	0.1-0.5 ml, via stomach tube	hexachloroethane	0.005 mg/g (240 min.)	liver	F-7
	rabbit	1.0 ml/kg, via stomach tube	hexachloroethane	trace (6 hrs)	bile	F-5
				5.5 ng/g (24 hrs)		
				trace (48 hrs)		

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
o-Chlorobenzaldehyde	cat	2.65 uM *in vitro* blood tests	unchanged	50% (half-life) (70 sec.)	blood	G-1
	man	2.65 uM *in vitro* blood tests	unchanged	50% (half-life) (15 sec.)	blood	
	rat	2.65 uM *in vitro* blood tests	unchanged	50% (half-life) (15 sec.)	blood	
Chlorobenzene	rabbit	150 mg/kg, via stomach tube	urinary metabolites, total	72.2%	urine	H-1
			glucuronide	25.2%		
			ethereal sulfate	26.6%		
			mercapturic acid	20.4%		
	rabbit	10 or 12 g chlorobenzene, via stomach tube	4-chlorocatechol (ethereal sulphate and glucuronide conjugates)	major metabolite (2 days)	urine	H-2
			p-chlorophenyl-mercapturic acid	major metabolite (2 days)	urine	
			p-chlorophenol and p-chlorophenol-glucuronide	0.5% (2 days)	urine	
			3,4-dihydro-3,4-dihydroxychlorobenzene	0.03% (2 days)	urine	
	rabbit	0.5 g chlorobenzene/kg, oral	catechol derivatives	37%	urine	H-3

Compound	Species	Rate and Route of administration	Metabolites: Compound	Percent of dose	Site	Ref.
Chlorobenzene (continued)	rabbit	0.5 g chlorobenzene/kg, oral	mercapturic acids	28%	urine	
			p-chlorophenol	2-3%	urine	
			o-chlorophenol	trace	urine	
	rabbit	0.5 g chlorobenzene/kg, oral	catechols	27%	urine	H-4
			mercapturic acids	27%	urine	
	rabbit	0.5 g chlorobenzene/kg, oral	chlorobenzene (unchanged)	27%	expired air	G-3
	rabbit	0.5 g chlorobenzene/kg, oral	chlorobenzene (unchanged)	27%	expired air	G-4
	rabbit	0.5 g ^{14}C-chlorobenzene, orally, twice daily for four days	^{14}C-activity	19.6% 2.6% 0.005%	urine feces body tissues	G-5
(a) urinary metabolites are expressed as percentage of urinary ^{14}C-activity			urinary metabolites[a]			
			3,4-dihydro-3,4-dihydroxy-chlorobenzene	0.57%[a]	urine	
			monophenols	2.84%[a]		
			diphenols	4.17%[a]		
			mercapturic acids	23.80%[a]		
			ethereal sulphates	33.88%[a]		
			glucuronides	33.57%[a]		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Chloroform	mouse	60 mg/kg, orally	CO_2	80% (24 hrs)	expired breath	I-1
			bicarbonate/carbonate	13% (24 hrs)	urine	
	rat	60 mg/kg, orally	CO_2	66% (24 hrs)	expired breath	I-1
(a) combined with toluene soluble metabolites			chloroform[a]	20% (24 hrs)	expired breath	
	monkey	60mg/kg, orally	CO_2	18% (24 hrs)	expired breath	I-1
	mouse	60 mg/kg, oral dose, daily for 5 days	CO_2	80% (48 hrs)	expired breath	I-2
			chloroform, (unchanged)	6% (48 hrs)	expired breath	
	rat	(60 mg/kg, oral dose, daily for 5 days)	CO_2	66% (48 hrs)	expired breath	I-2
			chloroform, unchanged	20% (48 hrs)	expired breath	
	monkey	60 mg/kg, oral dose, daily for 5 days	CO_2	16% (48 hrs)	expired breath	I-2
			chloroform, unchanged	79% (48 hrs)	expired breath	
(b) range of adults, 18 to 50 years old, weighing 60 to 80 kg.	human[b] (male)	500 mg/orally	chloroform, unchanged	17.8-66.6% (8 hrs)	expired air	I-3
			CO_2	50.6% (8 hrs)	expired air	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Percent of dose	Site	Ref.
Chloroform (continued)	(female)[b]	500 mg/orally	chloroform, unchanged	25.6-40.4% (8 hrs)	expired air	I-3
			CO_2	48.5% (8 hrs)	expired air	
	human	5 mg, single breath inhalation	chloroform	10%	expired air	I-4
		1-Cl napthalene isomer				
Chloronaphthalene	male albino rabbits (approx. 2 kilos in weight)	1 g/rabbit, by stomach tube	ethereal sulfate	10.1% (4 days)	urine	J-1
			mercapturic acids	13.1% (4 days)	urine	
			glucuronic acid	53.7% (4 days)	urine	
			free phenolic compounds	2% (4 days)	urine	
		1-Cl naphthalene isomer				
	Yorkshire pig (avg. 7.5 kg in weight)	300 mg/pig, retrocarotid administration	1-Cl naphthalene	6.7 ug/g (6 hours)	brain	J-2
				16.1 ug/g (6 hours)	kidney	
				2.3 ug/g (6 hours)	liver	
				1.0 ug/g (6 hours)	skeletal muscles	
				1.0 ug/g (6 hours)	lung	
				5.0 ug/g (6 hours)	psoas	
				1.5 ug/g (6 hours)	heart	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Chloronaphthalene (cont.)		1-Cl naphthalene isomer (cont.)				
	Yorkshire pig (avg. 7.5 kg in weight)	300 mg/pig, retrocarotid administration	4-Cl naphthol	1.4 ug/g (6 hours)	kidney	J-2
				1.0 ug/g (6 hours)	liver	
				440 ug/g (6 hours	urine	
				900 ug/g (6 hours)	bile	
		2-Cl napthalene isomer				
	Yorkshire pig (avg. 7.5 kg in weight)	300 mg/pig, retrocarotic administration	2-Cl naphthalene	21.4 ug/g (6 hours)	brain	
				14.4 ug/g (6 hours)	kidney	
				5.2 ug/g (6 hours)	liver	
				2.2 ug/g (6 hours)	skeletal muscle	
				0.8 ug/g (6 hours)	lung	
				4.5 ug/g (6 hours)	psoas	
				4.5 ug/g (6 hours)	heart	
				0.6 ug/g (6 hours)	fat	
			3-Cl-2-naphthol	0.6 ug/g (6 hours)	kidney	
				0.7 ug/g (6 hours)	liver	
				60 ug/g (6 hours)	urine	
				260 ug/g (6 hours)	bile	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Chloronitrobenzene isomers	rabbit	ortho-isomer, 0.1 g/kg[a]	ether glucuronides	42%	urine	K-1
			ethereal sulphates[b] (aminochlorophenols and chloronitrophenols)	24%	urine	
			free chloroaniline	9%	urine	
				0.3%	feces	
			nitrophenylmercapturic acid	7%	urine	K-1
			free phenolics	trace amounts	urine	
	rabbit	meta-isomer, 0.2 g/kg[a]	ether glucuronide	33%	urine	K-1
			ethereal sulphates[b]	18%	urine	
			free chloroaniline	11%	urine	
				0.6%	feces	
			nitrophenylmercapturic acid	1%[c]	urine	
			free phenolics	trace amounts	urine	

(a) method of administration not reported

(b) See summary report for identification of aminochlorophenols and chloronitrophenols

(c) This amount was considered insignificant since it was within the normal range of mercapturic acid levels in urine.

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Chloronitrobenzene isomers (continued)	rabbit	para-isomer, 0.2 g/kg (a)	ether glucuronide	19%	urine	K-1
			ethereal sulphates(b)	21%	urine	
			free chloroaniline	9%	urine	
				small amount	feces	
			conjugated chloroaniline	4%	urine	
			nitrophenylmercapturic acid	7%(d)	urine	
			free phenolics	trace amount	urine	
			p-chloronitrobenzene, unchanged	small amount	feces	
(d) Measured by colorimetry. A lower value (3%) was obtained by modified Stekol method. See Ref. B-1 for details.						
Chloroprene	human	(a)	an epoxide(a)	(a)	liver	L-1
(a) Metabolism information was based on author's review of chloroprene toxicity reports. No experimental data was reported.						

Chlorotoluene - See Benzyl chloride

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Dichlorobenzene	rabbit	0.5 g/kg, via stomach tube (o-isomer)	glucuronide	48%	urine	M-1
			ethereal sulfate	21%	urine	
			mercapturic acid	5%	urine	
			monophenols	39%	urine	
			catechols	4%	urine	
			quinols	0%	urine	
		(m-isomer)	glucuronide	36%	urine	M-1
			ethereal sulfate	7%	urine	
			mercapturic acid	11%	urine	
			monophenols	25%	urine	
			catechols	3%	urine	
			quinols	0	urine	
		(p-isomer)	glucuronide	36%	urine	M-1
			ethereal sulfate	27%	urine	
			mercapturic acid	0%	urine	
			monophenols	35%	urine	
			catechols	0%	urine	
			quinols	6%	urine	
	rabbit	0.5 g/kg. via stomach tube (o-isomer)	3,4-dichlorophenol	30%	urine	M-2
			2,3-dichlorophenol	9%	urine	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Percent of dose	Site	Ref.
Dichlorobenzene (continued)	rabbits	0.5 g/kg, via stomach tube (o-isomer)	3,4- and 4,5-dichloro-catechols	4%	urine	M-2
			3,4-dichlorophenyl-mercapturic acid	5%	urine	
	rabbit	0.5 g/kg, via stomach tube (m-isomer)	2,4-dichlorophenol	20%	urine	M-1
			3,5-dichlorophenol	minor amount	urine	
			3,5-dichlorocatechol	minor amount	urine	
			2,4-dichlorophenol-mercapturic acid	minor amount	urine	
	rabbit	0.5 g/kg, via stomach tube	2,5-dichlorophenol	35%	urine	M-2
			2,5-dichloroquinol	6%	urine	
1,2- Dichloroethane	mouse	0.05, 0.10, 0.14 or 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p. injection	^{14}C-1,2-dichloro-ethane, unchanged	10-42% (3 days)	expired breath	N-1
			$^{14}CO_2$	12-15% (3 days)	expired breath	
			^{14}C-activity	0-0.6% (3 days)	feces contaminated with urine	
				0.6-1.3% (3 days)	whole-body homogenate	
			^{14}C-activity, urinary	51-73% (total, 3 days)	urine	
			chloroacetic acid	6-23%(a) (3 days)	urine	

(a) figures represent percentage of radioactivity

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
1,2- Dichloroethane (continued)	mouse	0.05, 0.10, 0.14 or 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p. injection	S-carboxymethyl-cysteine free	44-46%[a] (3 days)	urine	N-1
			conjugated	0.5-5%[a] (3 days)	urine	
		0.05-0.17 g/kg, ^{14}C-1,2-dichloroethane, i.p. injection	thiodiacetic acid	33-34%[a] (3 days)	urine	
			2-chloroethanol	0.0-0.8%[a] (3 days)	urine	
			S,S'-ethylene-bis-cysteine	0.7-1.0%[a] (3 days)	urine	
	rat	100 mg, stomach tube	S-(beta-hydroxyethyl) mercapturic acid	major metabolite[b]	urine	N-2
(b) exact amounts were not reported			S-(beta-hydroxyethyl) cysteine	trace amounts[b]	urine	
1,1-Dichloroethylene (vinylidene chloride;1,1-DCE)	rat	0.5 mg (^{14}C)-1,1-DCE per kg, oral dose	(^{14}C)1,1-DCE (unchanged)	0.9% (72 hrs)	expired breath	O-1
			$^{14}CO_2$	23% (72 hrs)	expired breath	
			^{14}C-activity (primarily thiodiglycollic acid)	52% (72 hrs)	urine	
				2-4% (72 hrs)	liver and other tissues	
	rat	50 mg (^{14}C) 1,1-DCE per kg, oral dose	(^{14}C)1,1-DCE (unchanged)	20% (72 hrs)	expired breath	O-1

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1-Dichloroethylene (vinylidene chloride) (continued)	rat	50 mg (^{14}C) - 1,1-DCE per kg, oral dose)	$^{14}CO_2$	6% (72 hrs)	expired breath	O-1
			^{14}C-activity (primarily thiodiglycollic acid)	36% (72 hrs)	urine	
	rat	0.5 or 50 mg (^{14}C)-1,1-DCE per kg, oral dose	residual ^{14}C-activity	2-4% (72 hrs)	liver and other tissues	D-1
(a) represents metabolized 1,1-DCE; metabolites were not identified	rat (fasted or fed)	1 mg (^{14}C)1,1-DCE per kg, oral dose	^{14}C-activity(a)	97-99% (72 hrs)	total elimination(b)	O-2
		50 mg (^{14}C) - 1,1-DCE per kg, oral dose	^{14}C activity(a)	60-75% (72 hrs)	total elimination(b)	O-2
(b) primarily eliminated in urine		10 ppm (^{14}C)-1,1-DCE, 6 hrs inhalation	^{14}C-activity(a)	97-99% (72 hrs) after exposure	total elimination(b)	O-2
		200 ppm (^{14}C)-1,1-DCE 6 hrs inhalation	^{14}C-activity(a)	92% (72 hrs. after exposure, fasted rats)	total elimination(b)	O-2
				96% (72 hrs. after exposure, fed rats)	total elimination(b)	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1-Dichloroethylene (vinylidene chloride) (continued)	mouse	50 mg (^{14}C) 1,1-DCE per kg, oral dose	(^{14}C)1,1-DCE unchanged	6%	expired air	0-3
			$^{14}CO_2$	3%	expired air	
			chloroacetic acid	0	urine	
			thiodiglycollic acid	3%	urine	
			thioglycollic acid	5%	urine	
			dithioglycollic acid	23%	urine	
			thioglycollyloxalic acid	3%	urine	
			N-acetyl-S-cysteinyl acetyl derivative	50%	urine	
			N-acetyl-S-(2-carboxy-methyl)cysteine	4%	urine	
			urea	3%	urine	
	rat	50 mg (^{14}C)-1,1-DCE per kg, oral dose	(^{14}C)1,1-DCE, unchanged	28%	expired air	0-3
			$^{14}CO_2$	3.5%	expired air	
			chloroacetic acid	1%	urine	
			thiodiglycollic acid	22%	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1-Dichloroethylene (vinylidene chloride) (continued)	(rat)	(50 mg (^{14}C) 1,1-DCE per kg, oral dose)	thioglycollic acid	3%	urine	(0-3)
			dithioglycollic acid	5%	urine	
			thioglycollyloxalic acid	2%	urine	
			N-acetyl-S-cysteinyl acetyl derivative	28%	urine	
			N-acetyl-S-(2-carboxy-methyl)cysteine	0	urine	
			urea	3.5%	urine	
1,2-Dichloroethylene cis-isomer	rat liver	55 nmol/ml of homogenate, by perfusion	dichloroacetic acid	1-3% of total uptake(a)	in vitro	P-1
(a) total uptake of cis-1,2-DCE was about 25 nmol/ml			dichloroethanol	8-10% of total uptake(a)	in vitro	
trans-isomer	rat liver	55 nmol/ml of homogenate, by perfusion	dichloroacetic acid and dichloroethanol	0.5-1% of total uptake(b)	in vitro	P-1
(b) total uptake of trans-1,2-DCE was about 10 nmol/ml						

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
1,2-Dichloropropane	rabbit	1,500 ppm in air (7 hrs per day for 5 days)	dichloropropane	0.6-1.1 mg/ 100 cc blood	blood	Q-1
	rabbit	2,200 ppm in air (7 hrs per day for 5 days)	dichloropropane	1.5-2.9 mg/ 100 cc blood	blood	
	dog	1,000 ppm in air (7 hrs per day for 5 days)	dichloropropane	1.3-1.6 mg/ 100 cc blood	blood	Q-1
(a) Present in urine, but not identified or quantitated	rat, mouse, guinea pig	dichloropropane vapors (concentration not specified)	pigment-producing substance[a]	(a)	urine	Q-1
	rat	0.88 mg (8.5 uCi) of 1,2-dichloro(1-^{14}C)-propane in 0.5 ml arachis oil, single dose, via stomach tube	radioactive substance (unidentified)	50.2% (24 hrs)	urine	Q-2
				4.9-6.9% (96 hrs)	feces	
				3.2-4.1% (96 hrs)	carcass	
				1.4-1.7% (96 hrs)	skin	
				0.5% (96 hrs)	gut	
(b) probably unchanged 1,2-dipropane	rat	1.07 mg (10.3 uCi) of 1,2-dichloro-(1-^{14}C) propane, single oral dose	volatile chlorinated hydrocarbon [b]	23.1%	expired air	Q-2
			$^{14}CO_2$	19.3%	expired air	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Hexachlorobutadiene	albino mice, white rats, guinea pigs	unspecified	hexachlorobutane	unspecified	unspecified	R-1
		unspecified	pentachlorobutane	unspecified	unspecified	R-1
	mice	oral (5 mg/kg)	hexachlorobutadiene	17.4 ug (1 hour)	liver	R-2
				28.8 ug (2 hours)		
			hexachlorobutadiene	14.5 ug (3 hours)	brain	
				59.2 ug (24 hours)		
				11.4 ug (96 hours)		
Hexachloroethane	rabbit	0.5 g of ^{14}C-hexachloroethane per kg body wt., in diet	trichloroethanol	1.3% (3 days)	urine	S-1
			trichloroacetic acid	1.3% (3 days)	urine	
			dichloroacetic acid	0.8% (3 days)	urine	
			monochloroacetic acid (highly toxic)	0.7% (3 days)	urine	
			dichloroethanol	0.4% (3 days)	urine	
			oxalic acid	0.1% (3 days)	urine	

Compound	Rate and Route Species	of administration	Metabolites Compound	Percent of dose	Site	Ref.
Hexachloroethane (continued)						
	rabbit	0.5 g of ^{14}C-hexachloroethane per kg body wt., in diet	volatile metabolites (included CO_2, C_2Cl_6, tetrachloroethylene and 1,1,2,2-tetrachloroethane)	14-24% (3 days)	expired air	S-1
(a) sheep #1-10	sheep[a]	0.5 g/kg, single oral dose	hexachloroethane	10-28 ug/ml (24 hrs)	blood	S-2
			tetrachloroethylene	0.6-1.1 ug/ml (24 hrs)	blood	
			pentachloroethane	0.15-0.50 ug/ml (24 hrs)	blood	
(b) sheep #11 and 12. 96-hr metabolite levels were very low or nil; see Table 2 in ref. M-2	sheep[b]	0.5 g/kg, single oral dose	hexachloroethane	780-1260 ug (24 hrs)	feces	S-2
				50-70 ug (24 hrs)	urine	
			tetrachloroethylene	854-1300 ug (24 hrs)	feces	
				25-29 ug (24 hrs)	urine	
			pentachloroethane	trace-468 ug (24 hrs)	feces	
				20-25 ug (24 hrs)	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Hexachloroethane (continued)						
(c) Sheep #27 and 28, anaesthetized. See Table 3, ref. M-2 for additional details	sheep[c]	0.5 g/kg, single oral dose	hexachloroethane	1.7-2.2 ug/g (4 hrs)	bile	S-2
				0.2 ug/g (6 hrs)	blood	
				trace-1.1 ug/g (8.5 hrs)	fat	
				trace-0.04 ug/g (8.5 hrs)	muscle	
	sheep[c]	0.5 g/kg, single oral dose	hexachloroethane	trace-0.2 ug/g (8.5 hrs)	brain, kidney and liver	S-2
			tetrachloroethylene	0.3-0.5 ug/g (4 hrs)	bile	
				0.2-0.4 ug/g (6 hrs)	blood	
				0.6-2.1 ug/g (8.5 hrs)	fat	
				trace-0.5 ug/g (8.5 hrs)	muscle	
				trace-2.8 ug/g (8.5 hrs)	brain, kidney and liver	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Hexachloroethane (continued)						
	sheep[c]	.5 g/kg single oral dose	pentachloroethane	0-trace (4 hrs)	bile	S-2
				0-trace (6 hrs)	blood	
				0-0.02 ug/g (8.5 hrs)	fat	
				trace-0.01 ug/g(8.5 hrs)	muscle	
	sheep[c]	0.5 g/kg, single oral dose	pentachloroethane	trace-0.02 ug/g (8.5 hrs)	brain, kidney and liver	
	fresh liver slices, in olive oil emulsion, 37°C	18 mg/l added to emulsion	hexachloroethane	13.3 ug/g (4 hrs)	in vitro	S-2
			tetrachloroethylene	9.1 ug/g (4 hrs)	in vitro	
			pentachloroethane	0.76 ug/g (4 hrs)	in vitro	
	heated liver slices (5 min., 70°C), in olive oil emulsion	18 mg/l added to emulsion	hexachloroethane	50.8 ug/g (4 hrs)	in vitro	S-2
			tetrachloroethylene	2.4 ug/g (4 hrs)	in vitro	
			pentachloroethane	1.74 ug/g (4 hrs)	in vitro	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Hexachloroethane (continued)						
	fresh liver slices in olive oil emulsion, 37°C	54 mg/l added to emulsion	hexachloroethane	56.4 ug/g (4 hrs)	in vitro	S-2
			tetrachloroethylene	56.4 ug/g (4 hrs)	in vitro	
			pentachloroethane	0.95 ug/g (4 hrs)	in vitro	
	heated liver slices (5 min, 70°C), in olive oil emulsion	54 mg/l added to emulsion	hexachloroethane	20.2 ug/g (4 hrs)	in vitro	S-2
			tetrachloroethylene	0.36 ug/g (4 hrs)	in vitro	
			pentachloroethane	0.12 ug/g (4 hrs)	in vitro	
Methylene chloride	rat	412-930 mg (^{14}C)-methylene chloride/kg, intraperitoneal injection	^{14}C-activity (a)	77.9, 93.2(b) (2 hrs)	breath	T-1
				98.6, 96.8(b) (8 hrs)		
(a) represents ^{14}C-methylene chloride and metabolites				98.2 (24 hrs)		
				3.09 (2 hrs)	carcass	
(b) figures represent individual values for each experimental animal				2.06, 2.42(b) (8 hrs)		

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Methylene chloride (continued)						
	rat	412-930 mg $^{(14}$C)-methylene chloride/kg, intraperitoneal injection	^{14}C-activity(1)	1.53 (24 hrs)	carcass	T-1
				less than 0.01 (2 hrs and 8 hrs)	urine and feces	
				1.06 (24 hrs)	urine	
				.07 (24 hrs)	feces	
(b) figures represent individual values for each experimental animal	rat	412-930 mg (^{14}C)-methylene chloride/kg intraperitoneal injection	methylene chloride	77.0, 92.0(b) (2 hrs)	breath	T-1
				95.3, 92.6(b) (8 hrs)		
				91.50 (24 hrs)		
			carbon dioxide	0.44, 0.65(b) (2 hrs)	breath	
				1.44, 1.61(b) (8 hrs)		
				3.04 (24 hrs)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Methylene chloride (continued)						
(b) figures represent individual values for each experimental animal	rat	412-930 mg(^{14}C)-methylene chloride/kg, intraperitoneal injection	carbon monoxide	0.14, 0.14(b) (2 hrs)	breath	T-1
				1.16, 1.69(b) (8 hrs)		
(c) dpm x 10^3 g tissue, wet weight				2.15 (24 hrs)		
			^{14}C activity (unidentified compound)	0.34, 0.46(b) (2 hrs)	breath	
				0.74, 0.86(b) (8 hrs)		
				1.49 (24 hrs)		
			^{14}C- activity	15.1 (c) (2 hrs)	liver	T-1
				40.4, 40.2 (b,c) (8 hrs)		
				18.3 (c) (24 hrs)		
				11.1 (c) (2 hrs)	kidney	
				21.4, 23.2 (b,c) (8 hrs)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Methylene chloride (continued)						
(b) figures represent individual values for each experimental animal	rat	412-930 mg (^{14}C)-methylene chloride/kg, intraperitoneal injection	^{14}C-activity	7.4 (c) (24 hrs)		
				16.2 (c) (2 hrs)	adrenal glands	
(c) dpm x 10^3 g tissue, wet weight				15.4, 15.3 (b,c) (8 hr)		
				8.7 (c) (24 hrs)		
				7.5 (c) (2 hrs)	intestinal mesenteries	
				14.2, 15.3 (b,c) (8 hrs)		
				4.4 (c) (24 hrs)		
				14.8 (c) (2 hrs)	fat	T-1
				10.8, 36.5 (b,c) (8 hrs)		
				3.3 (c) (24 hrs)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Methylene chloride (continued)						
(c) dpm x 10^3 g tissue, wet weight	rat	412-930 mg (^{14}C)-methylene chloride/kg, intraperitoneal injection		2.2-3.8 (b,c) (2 hrs) 2.1-7.8 (c) (8 hrs) 2.1-5.5 (c) (24 hrs)	lung, heart, brain, stomach, small & large intestines	T-1
	rat	0.2 mmol/kg ^{14}C-methylene chloride, inhalation (8 hours), closed rebreathing system	carbon monoxide	47%	breath	T-2
			carbon dioxide	29%	breath	
	human	213 ppm methylene chloride inhalation (60 min)	carboxyhemoglobin (COHb)	1.5% COHb saturation (after 30 min of exposure) 1.75% COHb saturation (after 60 min of exposure) 2.4% COHb saturation (3 hrs after exposure)	blood	T-3

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Methylene chloride (continued)						
	human	986 ppm, inhalation (2 hrs)	carboxyhemoglobin (COHb)	10% blood COHb saturation 1 hr post-exposure	blood	T-3
	human	180-200 ppm, workroom air (8 hrs)	carboxyhemoglobin (COHb)	9% COHb blood saturation (after 8 hrs exposure)	blood	T-4
	rat	3.0 mmol/kg, intraperitoneal injection	carboxyhemoglobin (COHb)	6% maximum saturation (after 2-2.5 hrs)	blood	T-5
	rat	440 ppm, inhalation exposure (3 hr)	carboxyhemoglobin (COHb)	7% maximum saturation	blood	T-6
Pentachloroanisole (PCA)	rainbow trout	0.024 mg ^{14}C PCA/L water, at 12°C for 12 hrs.	pentachloroanisole	approx. 80 ug/g (after 12 hrs exposure)	fat	U-1
				approx. 3 ug/g (after 12 hrs exposure)	liver	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Pentachloroanisole (PCA) (continued)						
	rainbow trout	0.024 mg ^{14}C PCA/L water, at 12°C for 12 hours	pentachloroanisole	approx. 2 ug/g (after 12 hrs exposure)	muscle	U-1
				approx. 1 ug/g (after 12 hrs exposure)	blood	
	rainbow trout	0.05 mg ^{14}C PCA/L water, at 12°C for 24 hrs	pentachlorophenol glucuronide	10 ug/g	bile	U-1
Pentachlorobenzene	rabbit	0.5 mg/kg, by stomach tube	tri- or penta-chlorophenol	0.2% (3 days)	urine	V-1
				0.2% (4 days)		
(a) dose (0.5 mg/kg) was administered by subcutaneous injection				0.7%(a) (10 days)		
			other phenols	1% (3 and 4 days)	urine	
				1%(a) (10 days)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Pentachlorobenzene (continued)	rabbit	0.5 mg/kg, by stomach tube	pentachlorobenzene, unchanged	0 (3 and 4 days)	expired air	V-1
(a) dose (0.5 mg/kg) was administered by subcutaneous injection				0[a] (10 days)		
			other chloro-hydrocarbons	9% (3 days)	expired air	
				21% (4 days)		
				2%[a] (10 days)		
			pentachlorobenzene	5% (3 days)	feces	
				5% (4 days)		
				1.5%[a] (10 days)		
			pentachlorobenzene	45% (3 days)	gut contents	V-1
				31% (4 days)	gut contents	
				0.5%[a] (10 days)		
			pentachlorobenzene	1% (3 days)	pelt	
				5% (4 days)	pelt	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Pentachlorobenzene (continued)						
	rabbit	0.5 mg/kg, by stomach tube	pentachlorobenzene	47%(a) (10 days)	pelt	V-1
				15% (3 days)	depot fat	
				9% (4 days)		
				22(a) (10 days)		
			pentachlorobenzene	6% (3 days)	rest of body	
				5.5% (4 days)		
				10(a) (10 days)		
	rat	unspecified	unchanged(b)	3%	total excretion products (urine plus feces)	V-2
			pentachlorophenol(b)	9%	total excretion products (urine plus feces)	

(a) dose (0.5 mg/kg) was administered by subcutaneous injection

(b) results obtained from a preview article, the study manuscript is in publication preparation

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Pentachlorobenzene (continued)	rat	unspecified	tetrachlorophenol[b]	unspecified	total excretion products (urine plus feces)	V-2
			tetrachloro-hydroquinone	unspecified	total excretion products (urine plus feces)	
			a hydroxylated chlorothio-compound	unspecified	total excretion products (urine plus feces)	
Pentachloroethane	mouse	20 uL, injected subcutaneously	pentachloroethane (unchanged)	approx. 29% (24 hrs)	urine, feces, and expired air combined	W-1
			tetrachloroethylene	approx. 4% (24 hrs)	same as above	
			trichloroethanol	approx. 12% (24 hrs)	same as above	
			trichloroacetic acid	approx. 5% (24 hrs)	same as above	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Pentachloroethane (continued) (a) amount was not quantitated, but appeared to be a little less than the amount of tetrachloro-ethylene.	(mouse)	(20 ul, injected subcutaneously)	trichloroethylene	less than 5% (a) (24 hrs)	(urine, feces, and expired air combined)	(W-1)
	sheep	0.3 ml/kg, single oral dose	pentachloroethane	approx. 10^{-6} g/ml of plasma (day 3)	venous blood	W-2
			tetrachloroethylene	less than 10^{-5} g/ml of plasma (day 3)	venous blood	
	mouse	1.1-1.8 g/kg, injected sub-cutaneously	pentachloroethane (unchanged)	12-51% (3 days)	expired air	W-3
			trichloroethanol	16-32% (3 days)	urine	
			trichloroacetic acid	9-18% (3 days)	urine	
			trichloroethylene	2-16% (3 days)	expired air	
			tetrachloroethylene	3-9% (3 days)	expired air	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachlorobenzene		1,2,3,4-isomer				
	rabbit	300 mg/rabbit (male, 4-5 kg), by ip injection	2,3,4,5-tetra-chlorophenol	20% (10 days)	urine	X-1
			2,3,4,6-tetra-chlorophenol	2% (10 days)	urine	
	rabbit	.5 g/kg (chinchilla doe), by stomach tube	tetrachloro-phenols (2,3,4,5-tetra-chlorophenol)	43% (6 days)	urine	X-2
			other phenols	less than 1% (6 days)	urine	
			1,2,3,4-tetrachloro-benzene, unchanged	8% (6 days)	expired air	
			other chloro-benzenes	2% (2 days)	expired air	
			1,2,3,4-tetrachloro-benzene, unchanged	5% (6 days)	feces	
				10%, total (6 days)	tissues	
				0.1%	liver	
				2%	skin	
				5%	depot fat	
				0.5%	gut con-tents	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachlorobenzene (continued)	rabbit	(1,2,3,4-isomer) (continued)	1,2,3,4-tetrachlorobenzene, unchanged	2.0%	rest of body	X-2
		1,2,3,5-isomer				
	rabbit	300 mg/rabbit (male, 4-5 kg), by ip injection	2,3,4,5-tetrachlorophenol	3% (10 days)	urine	X-1
			2,3,5,6-tetrachlorophenol	2% (10 days)	urine	
			2,3,4,6-tetrachlorophenol	1.5% (10 days)	urine	
	rabbit	.5 g/kg (chinchilla doe), by stomach tube	tetrachlorophenols (predominantly 2,3,4,6-tetrachlorophneol)	5% (6 days)	urine	X-2
			other phenols	5% (6 days)	urine	
			1,2,3,5-tetrachlorobenzene, unchanged	12% (6 days)	expired air	
			other chlorobenzenes	9% (6 days)	expired air	
			1,2,3,5-tetrachlorobenzene, unchanged	14% (6 days)	feces	
				23% (6 days)	tissues	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Tetrachlorobenzene (continued)		(1,2,3,5-isomer) (continued)				
	rabbit	.5 g/kg (chinchilla doe), by stomach tube	1,2,3,5-tetrachlorobenzene, unchanged	0.5%	liver	X-2
				0.2%	brain	
				5%	skin	
				11%	Depot fat	
				1.4%	Gut contents	
				5.2%	rest of body	
		1,2,4,5-isomer				
	rabbit	300 mg/rabbit (male, 4-5 kg), by ip injection	2,3,5,6-tetrachlorophenol	2%	urine	X-2
	rabbit	.5 g/kg (chinchilla doe), by stomach tube	tetrachlorophenols	2% (6 days)	urine	X-1
			other phenols	5% (6 days)	urine	
			1,2,4,5-tetrachlorobenzene, unchanged	2% (6 days)	expired air	
			other chlorobenzenes	10% (6 days)	expired air	
			1,2,4,5-tetrachlorobenzene, unchanged	16% (6 days)	feces	
			1,2,4,5-tetrachlorobenzene, unchanged	48% (6 days)	tissues	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachlorobenzene (continued)	rabbit	1,2,4,5-isomer .5 g/kg (chinchilla doe), by stomach tube	1,2,4,5-tetrachloro-benzene, unchanged	0.1%	liver	X-1
				0.1%	brain	
				10%	skin	
				25%	Depot fat	
				6.2%	Gut contents	
				6.4%	rest of body	
1,1,2,2-Tetrachloro-ethane	human	2.5 mg ^{38}Cl-tetrachloroethane, single breath inhalation	^{38}Cl-activity	3.3% (1 hr)	expired air	Y-1
	mouse	0.21-0.32 g ^{14}C-tetrachloroethane per kg body wt., intraperitoneal injection	$^{14}CO_2$	50% (3 days)	expired air	Y-2
			^{14}C-tetrachloroethane (unchanged)	4% (3 days)	expired air	
			^{14}C-activity	28% (3 days)	urine	
				less than 1% (3 days)	feces contaminated with urine	
				16% (3 days)	whole body homogenate	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
1,1,2,2-Tetrachloroethane (continued)						
	mouse	0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt.	trichloroethylene	0.2-0.4% (24 hrs)	expired air	
(a) figures express metabolites as percentage of urinary radioactivity			tetrachloroethylene	0.2-0.4% (24 hrs)	expired air	
			dichloroacetic acid	27%(a) (24 hrs)	urine	Y-2
			trichloroethanol	10%(a) (24 hrs)	urine	
			oxalic acid	7%(a) (24 hrs)	urine	
	mouse	0.16-0.32 g ^{14}C-tetrachloroethane per kg body weight	trichloroacetic acid	4%(a) (24 hrs)	urine	Y-2
			urea	2%(a) (24 hrs)	urine	
			glyoxylic acid	0.9%(a) (24 hrs)	urine	
	rat	200 ppm, inhalation exposure (8 hrs)	total trichloro-compounds	8.2 mg/kg (48 hrs)	urine	Y-3
			trichloroacetic acid	1.7 mg/kg (48 hrs)	urine	
			trichloroethanol	6.5 mg/kg (48 hrs)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,2,2-Tetrachloroethane (continued)						
	rat	200 ppm, inhalation exposure (8 hrs)	total trichloro-compounds	2.1 mg/kg (48 hrs)	urine	Y-3
				0.3 mg/kg (2nd 48-hr period)		
	rat	2.78 mmol tetrachloroethane per kg body wt (equivalent to 467 mg/kg(b))	trichloroacetic acid	1.3 mg/kg (48 hrs)	urine	Y-3
				0.3 mg/kg (2^{nd} 48-hr period)		
			trichloroethanol	0.8 mg/kg (48 hrs)	urine	
				immeasureable amount (2^{nd} 48-hr period)		

(b) conversion of 2.78 mmol to 467 mg/kg was reported in NIOSH criteria document on occupational exposure to 1,1,2,2-tetrachloroethane

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachloroethylene	rat	1.75 uCi ^{36}Cl-tetrachloroethylene administered by stomach tube	^{36}Cl-radioactivity	97.9% (48 hrs)	expired air	Z-1
				2.1% (18 days; urinary radioactivity consisted of trichloroacetic acid (0.6% of original dose) and inorganic chloride)	urine	
	rat liver	180 ppm vapor	trichloroacetic acid	10-15%	in vitro	Z-2
			trichloroacetic acid (bound to liver tissue)	3-5%	in vitro	
(b) absorbed radioactivity was equivalent to 70% of the dose	mouse	1.3 mg/g body weight (vapor, 2 hrs)	^{14}C-radioactivity	90% of absorbed activity(b)	expired air	Z-3
				20% of absorbed activity(b)	urine	
				less than 0.5% of absorbed activity(b)	feces	
(a) represents percentage of urinary radioactivity	mouse		trichloroacetic acid	52%(a)	urine	
			oxalic acid	11%(a)		
			dichloroacetic acid	trace amounts(a)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachloroethylene (continued)	rat	200 ppm, inhalation exposure (8 hrs)	trichloroacetic acid	5.3 mg/kg body weight (48 hrs)	urine	Z-4
			trichloroethanol	3.2 mg/kg body weight (48 hrs)	urine	
	rats	2.78 mmol/kg body wt., intraperitoneal injection	trichloroacetic acid	5.5 mg/kg body weight (48 hrs)	urine	Z-4
			trichloroethanol	0.08 mg/kg body weight (48 hrs)	urine	
(a) single animal results	mouse	2.78 mmol/kg body wt., intraperitoneal injection	trichloroacetic acid	23.7, 22.9 mg/L[a]	urine	Z-4
			trichloroethanol	0.1, 0.4 mg/L[a]	urine	
	human	20-70 ppm, occupational exposure	trichloroacetic acid	4-35 mg/L	urine	Z-4
			trichloroethanol	4-20 mg/L	urine	
	human	200-400 ppm, occupational exposure	trichloroacetic acid	32-97 mg/L	urine	Z-4
			trichloroethanol	21-100 mg/L	urine	
	human	87 ppm inhalation (3 hrs)	trichloroacetic acid	1.8% of retained tetrachloro-ethylene (67 hrs)	urine	Z-5

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachloroethylene (continued)	human	87 ppm inhalation (3 hrs)	unknown chloride	1.0% of retained tetrachloro-ethylene (67 hrs)	urine	Z-5
	human (male)	30-100 ppm, inhalation (8 hrs/day, 5 days/week, occupational exposure)	total trichlorocompounds	123.3 hrs biological half-life	urine	Z-6
	human (female)	10-20 ppm vapor (8 hrs/day, 5 days/week, occupational exposure)	total trichlorocompounds	190.1 hrs biological half-life	urine	
	human	100 ppm inhalation 7 hrs/day, 5 days	tetrachloroethylene	1 ppm (14 days after exposure)	breath	Z-7
			tetrachloroethylene	3 days expirational half-life	breath	
	rat	200 ppm 6 hrs/day, 4 days	tetrachloroethylene	622.2 nmol/g (17 hrs after last exposure)	perirenal fat	Z-8
				18.4 nmol/g (17 hrs after exposure)	cerebrum	
				13.1 nmol/g (17 hrs after exposure)	cerebellum	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Tetrachloroethylene (continued)	rat	200 ppm 6 hrs/day, 5 days	tetrachloroethylene	1724.8 nmol/g after 5th day/6 hrs exposure	perirenal fat	Z-8
				142.5 nmol/g after 5th day/6 hrs exposure	cerebrum	
				92.3 nmol/g after 5th day/6 hrs exposure	cerebellum	
Trichlorobenzene		1,2,3-isomer				
	rabbit	0.5 g/kg, by stomach tube; superior numbers indicate the number of trials	glucuronide	50%[3] (46-55%) (5 days)	urine	AA-1
			ethereal sulfate	12%[3] (9-13%) (5 days)	urine	
			total trichlorophenols	78%[4] (64-89%) (5 days)	urine	
			mercapturic acid (2,3,4-trichloro-phenylmercap-turic acid)	0.3%[3] (0.2-0.5%) (5 days)	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichlorobenzene (continued)		1,2,4-isomer				
	rabbit	0.5 g/kg, by stomach tube superior numbers indicate the number of trials	glucuronide	27%[3] (18-33%) (5 days)	urine	AA-1
			ethereal sulfate	11%[3] (10-12%) (5 days)	urine	
			total phenols	42%[3] (33-51%) (5 days)	urine	
			mercapturic acid (2,3,5- and 2,4,5-trichlorophenylmercapturic acids)	0.3%[3] (0.2-0.5%) (5 days)		
		1,3,5-isomer				
	rabbit	0.5 g/kg, by stomach tube; superior numbers indicate the number of trials	glucuronide	20%[5] (16-23%) (5 days)	urine	AA-1
			ethereal sulfate	3%[5] (1-5%) (5 days)	urine	
			total phenols	9%[5] (7-13%) (5 days)	urine	
			mercapturic acid	0%[2] (5 days)	urine	

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Trichlorobenzene (continued)		1,3,5-isomer				
	rabbit	1.5 g/rabbit (unspecified weight)	1,3,5-trichloro-benzene	9% (2 days)	feces	AA-1
	rabbit	0.5 g/kg, by stomach tube	trichloro-phenol	3% (8 days)	urine	AA-2
				10% (9 days)		
			other phenols (including 4-chlorophenol and 4-chlorocatechol)	1% (8 days) 4% (9 days)	urine	
			1,3,5-trichloro-benzene, unchanged	12% (8 days)	expired air	
				8.5% (9 days)		
			other chloro-hydrocarbons	0.6% (8 days)	expired air	AA-2
				1.5% (9 days)		
			1,3,5-trichloro-benzene, unchanged	13% (8 days)	feces	
				1.5% (9 days)	feces	
				23% (8 days)	gut contents	
				18% (9 days)		

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
Trichlorobenzene (continued)		1,3,5-isomer				
	rabbit	0.5 g/kg, by stomach tube	1,3,5-trichlorobenzene, unchanged	5% (8 days)	pelt, including subcutaneous fat	AA-2
				5% (9 days)		
				5% (8 days)	depot fat	
				4.5% (9 days)		
				22% (8 days)	rest of body	
				20% (9 days)		
1,1,1-Trichloroethane	rat	700 mg 1,1,1-trichloroethane-1-C^{14} per kg, injected intraperitoneally	1,1,1-trichloroethane-1-C^{14}, unchanged	98.7% (25 hrs)	expired air	AB-1
			$^{14}CO_2$	0.5% (25 hrs)	expired air	
			^{14}C-activity, primarily 2,2,2-trichloroethanol-2-C^{14}glucuronide	0.85% (25 hrs)	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)						
	rat	700 mg 1,1,1-trichlor-ethane-1-C^{14} per kg, injected intraperitoneally	^{14}C-activity, at least 90% unchanged 1,1,1-trichloro-ethane 1-1-C^{14}	0.08-0.12% (25 hrs)	skin	AA-2
			^{14}C-activity	0.02% (25 hrs)	blood	
				0.02% (25 hrs)	fat	
			^{14}C-activity	0.03% (25 hrs)	feces	
				trace amounts	liver, intestines, kidneys, heart, lung, brain, muscle, and hair	
		200 ppm, inhalation (8 hrs)	trichloroethanol	3.1 mg/kg body (48 hrs)	urine	AB-2
			trichloroacetic acid	0.5 mg/kg body weight (48 hrs)	urine	
	rat	2.78 mmol/kg body weight, intraperi-toneal injection	trichloroethanol	3.5 mg/kg body weight (48 hrs)	urine	AB-2

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane	rat	2.78 mmol/kg body	trichloroethanol	immeasurable amount (2^{nd} 48 hr period)		
			trichloroacetic acid	0.5 mg/kg body weight (48 hrs)	urine	
				0.3 mg/kg body weight (2^{nd} 48 hr period)		
	rat	221 ppm, inhalation (4 hrs)	trichloroethanol	126.2 ug, total (24 hrs)	urine	AB-3
				7.5 ug, total (2^{nd} 24 hr period)		
	rat	221 ppm, inhalation (4 hrs)	trichloracetic acid	3.2 ug, total (24 hrs)	urine	AB-3
				8.1 ug, total (2^{nd} 24-hr period)		
			1,1,1-trichloroethane	2.488 mg (1^{st} hr post-exposure)	expired air	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)	rat	221 ppm, inhalation	1,1,1-trichloroethane	0.050 mg (8^{th} hr post-exposure)	expired air	AB-3
	rat	443 ppm, inhalation (4 hrs)	trichloroethanol	206.5 ug, total (24 hrs)	urine	AB-3
				8.5 ug (2^{nd} 24 hr period		
			trichloroacetic acid	9.5 ug (24 hrs)	urine	
				10.6 ug (2^{nd} 24 hr period)		
		443 ppm, inhalation (4 hrs)	1,1,1-trichloroethane	5.719 mg (1^{st} hr post-exposure)	expired air	AB-3
				0.098 mg (8^{th} hr post-exposure)		
		204 ppm, inhalation (8 hrs/day, 5 days/week, for 14 weeks)	trichloroethanol	93 ug/24 hrs (1^{st} week)	urine	AB-3
				435 ug/24 hrs (10^{th} week)	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)	rat	204 ppm, inhalation (8 hrs/day, 5 days/week, for 14 weeks)	trichloroethanol	0.059-0.88 ug/ml (determined periodically, 14 weeks)	blood	
			trichloroacetic acid	12-20 ug/ 24 hrs (weekly)	urine	
			1,1,1-trichloroethane	0.677-1.000 ug/ml (determined periodically, 14 weeks)	blood	
	human	5 mg ^{38}Cl-1,1,1-trichloroethane, inhalation (single breath)	^{38}Cl-radioactivity	44% (1 hr)	expired air	AB-4
	human	250 ppm, inhalation (30 minutes per exposure, at rest and with consecutive work loads of 50, 100, and 150 W)	1,1,1-trichloroethane	3.0 ppm (at rest)	arterial blood	AB-5
				4.5 ppm (50 W)		
				5.2 ppm (100 W)		
	human			5.5 ppm (150 W)		
				1.4 ppm (at rest)	venous blood	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)						
	human		1,1,1-Trichloroethane	3.1 ppm (50 W)	venous blood	AB-5
				3.5 ppm (100 W)		
				4.4 ppm (150 W)		
				125 ppm (at rest)	alveolar air	
				168 ppm (50 W)		
				210 ppm (100 W)		
				207 ppm (150 W)		
	human	350 ppm, inhalation (30 minutes per exposure, at rest and with 50 W work-load)	1,1,1-trichloroethane	5.0 ppm (at rest)	arterial blood	AB-5
				7.2 ppm (50 W)		
				3.0 ppm (at rest)	venous blood	
				5.5 ppm (50 W)		
				179 ppm (at rest)	alveolar air	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)	human	350 ppm, inhalation (30 minutes per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2)	1,1,1-trichloroethane	239 ppm (50 W)	arterial blood	AB-5
		250 ppm, inhalation (30 minutes per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2)	1,1,1-trichloroethanol	2.2 ppm (at rest)	arterial blood	
				3.3 ppm (at rest plus 4% CO_2)		
				3.9 ppm (50 W plus 4% CO_2)		
				1.0 ppm (at rest)	venous blood	
				1.2 ppm (at rest plus 4% CO_2)		
				1.9 ppm (50 W plus 4% CO_2)		
	human	250 ppm, inhalation (30 minutes per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	1,1,1-trichloroethanol	128 ppm (at rest	alveolar air	AB-5
				176 ppm (at rest plus 4% (CO_2)		
				201 ppm (50 W plus 4% CO_2)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)	human	500 ppm, inhalation (6.5 7 hrs/day, 5 days)	trichloroethanol	20.1 mg/24 hrs (1st day)	urine	AB-6
				30.1 mg/24 hrs (2nd day)		
				29.3 mg/24 hrs (3rd day)		
				46.6 mg/24 hrs (4th day)		
				7.0 mg/24 hrs (6th day after last exposure)		
				less than 1.0 mg/24 hrs (12th day after last exposure)		
			trichloroacetic acid	7.5 mg/24 hrs (1st day)	urine	
				10.9 mg/24 hrs (2nd day)		
	human	500 ppm, inhalation 6.5 7 hrs/day, 5 days	trichloroacetic acid	12.3 mg/24 hrs 3rd day)	urine	AB-6
				14.1 mg/24 hrs (4th day)		
				18.0 mg/24 hrs (6th day after last exposure)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)						
	human	500 ppm, inhalation 6.5 7 hrs/day, 5 days	trichloroacetic acid	17.5 mg/24 hrs 12th day) after last exposure)	urine	AB-6
	human	4.3 ppm, inhalation (8 hrs/day, 5.5 days/week, at least 5 years)	total trichloro-compounds	2.0 mg/L	urine	AB-7
			trichloroethanol	1.2 mg/L	urine	
			trichloroacetic acid	0.6 mg/L	urine	
	human	24.6 ppm, inhalation (8 hrs/day, 5.5 days/week, at least 5 years)	total trichloro-compounds	8.2 mg/L	urine	AB-7
			trichloroethanol	5.5 mg/L	urine	
			trichloroacetic acid	2.4 mg/L	urine	
	human	53.4 ppm, inhalation (8 hrs/day, 5 1/2 days/week, at least 5 years)	total trichloro-compounds	13.9 mg/L	urine	AB-7
			trichloroethanol	9.9 mg/L	urine	
			trichloroacetic acid	3.6 mg/L	urine	
	rat	20 umol/L (500 ppm), inhalation (6 hrs/day, 4 days)	1,1,1-trichloroethane	16.9 nmol/g (17 hrs after last exposure)	perirenal fat	AB-8
				183.5-276.0 nmol/g (immediately after additional 2-6 hrs exposure)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,1-Trichloroethane (continued)	rat	20 umol/L (500 ppm), inhalation (6 hrs/day, 4 days)	1,1,1-trichloroethane	0.08-0.17 nmol/g (17 hrs after last exposure)	brain, liver, lung, blood (each)	AB-8
				7.9-21.3 nmol/g (immediately after 2-6 hrs additional exposure)		
(a) additonal exposure data are given in Table 6 of summary report on 1,1,1-Trichloroethane	mouse[a]	100 ppm, inhalation (0.5-24 hrs)	1,1,1-trichloroethane	3.5-14.0 ug/g	liver	AB-9
				3.0-8.1 ug/g	blood	
				4.3-10.0 ug/g	kidneys	
				4.4-9.2 ug/g	brain	
1,1,2-Trichloroethane (a) about 3/5 of the expired ^{14}C-activity was $^{14}CO_2$; 2/5 was unchanged 1,1,2-trichloroethane	mouse	0.1-0.2 g of ^{14}C-1,1,2-trichloroethane per kg, injected intraperitoneally	^{14}C-activity	16-22%[a] (3 days)	expired air	AC-1
				0.1-2% (3 days)	feces contaminated with urine	
				1-3% (3 days)	whole-body hemogenate	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
1,1,2-Trichloroethane (continued)						
	mouse		^{14}C-activity, urinary	73-87% (3 days)	urine	
(b) figures represent percentage of urinary radioactivity			chloroacetic acid	6-31%(b) (3 days)		
			S-carboxymethyl-cysetine	29-46%(b) free (3 days)		
				3-10%(b) conjugated (3 days)		
			thiodiacetic acid	38-42%(b) (3 days)		
			oxalic acid	0.3-0.5%(b) (3 days)		
	mouse	0.1-0.2 g of ^{14}C-1,1,2-tri-ethane per kg, injected intraperitoneally	2,2-dichloro-ethanol(b)	0.9-2.1% (3 days)	urine	AC-1
			2,2,2-trichloro-ethanol(b)	0.2% (mean) (3 days)		
			trichloroacetic acid(b)	1.4-2.3% (3 days)		
	rat	200 ppm, inhalation (8 hrs)	trichloroacetic acid	0.3 mg/kg body weight (48 hrs after exposure)	urine	AC-2

Compound	Species	Rate and Route of administration	Metabolites: Compound	Metabolites: Percent of dose	Metabolites: Site	Ref.
1,1,2-Trichloroethane (continued)						
	rat	200 ppm, inhalation (8 hrs)	trichloroethanol	0.3 mg/kg body weight (48 hrs after exposure)	urine	
	rat	2.78 mmol/kg body weight, injected intra-peritoneally	trichloroacetic acid	0.4 mg/kg body weight (48 hrs)	urine	AC-2
				0.3 mg/kg body weight (2^{nd} 48 hr period)		
			trichloroethanol	0.2 mg/kg body weight (48 hrs)	urine	
				immeasurable amount (2^{nd} 48 hr period)		
	human	about 5mg ^{38}Cl-1,1,2-tri-chloroethane, inhaled in single breath	^{38}Cl-radioactivity	2.9% (1 hr)	expired breath	AC-3
Trichloroethylene (TCE)	rat	10 mg/L air, inhalation (exposure period not stated)	trichloroethylene	41.3 mg%	blood cellular compon-ents	AD-1
				2.5 mg%	blood plasma	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	rat	4.0, 7.5, or 8.6 uCi of ^{36}Cl-TCE	trichloroethylene (unchanged)	72-85%	expired air	AD-2
	human	54 or 97 ppm, inhalation (8 hrs)	trichloroethylene (unchanged)	8% of retained TCE	expired air	AD-3
	human	250-380 ppm, inhalation (160 min.)	trichloroethylene (unchanged)	16% or retained TCE	expired air	AD-4
	human	27, 81,or 201 ppm, inhalation (4 hrs)	trichloroethylene (unchanged)	13-19% of retained TCE	expired air	AD-5
	human	70 or 140 ppm, with or without 100 W workload; inhalation (4 hrs)	trichloroethylene (unchanged)	10% (of retained TCE)	expired air	AD-6
	human	0.537 or 1.074 ppm, inhalation, at rest (30 min)	trichloroethylene	25% of inspired TCE concentration	expired air	AD-7
	human	inhalation, concentration not reported	trichloroethylene	27.7% of retained TCE, men	expired air	AD-8
				18.6% of retained TCE, women	expired air	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	human	500-850 ug/L air, inhalation (5 hrs)	trichloroethanol	50%, total amount excreted (350 hrs, average)	urine	AD-9
			trichloroacetic acid	19%, total amount excreted (387 hrs, average)	urine	
			monochloroacetic acid	4%, total amount excreted (112 hrs, average)	urine	
	human	1,042 ug/L air, inhalation (5 hrs)	trichloroethanol	45.4% (total, 3 weeks)	urine	AD-10
			trichloroacetic acid	31.9% (total, 3 weeks)	urine	
	human	54 or 97 ppm, inhalation (8 hrs)	trichloroethanol	32.7% (several weeks)	urine	AD-3

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	human	54 or 97 ppm, inhalation (8 hrs)	trichloroacetic acid	17.7% (several weeks)	urine	
	human	250-380 ppm, inhalation (160 min)	trichloroethanol	42.7-48.6% of retained TCE (6 days)	urine	AD-4
			trichloroacetic acid	32.6-43.9% or retained TCE (6 days)	urine	
	human	170 ppm inhalation (3 hrs)	trichloroethanol	53.1% (100 hrs)	urine	AD-11
			trichloroacetic acid	21.9% (100 hrs)	urine	
	human	170 ppm, inhalation (7 hrs with a 1-hr break)	trichloroethanol	44% (100 hrs)	urine	AD-11
			trichloroacetic acid	18.1% (100 hrs)	urine	
	human	1 mg/L air, inhalation (5 hrs)	trichloroethanol	46.1% (16 or 21 days)	urine	AD-12
			trichloroacetic acid	30.1% (16 or 21 days)	urine	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	human	10, 25, 50, 60, or 120 ppm, inhalation[a]	total trichloro-compounds	60.5 mg/L (10 ppm exposure)	urine	AD-13
				164.3 mg/L (25 ppm exposure)	urine	
				418.9 mg/L (50 ppm exposure)	urine	
				468.0 mg/L (60 ppm exposure)	urine	
				915.3 mg/L (120 ppm exposure)	urine	
			trichloroethanol	42.0 mg/L (10 ppm exposure)	urine	
				77.3 mg/L (25 ppm exposure)	urine	
				267.3 mg/L (50 ppm exposure)	urine	
				307.9 mg/L (60 ppm exposure)	urine	

(a) exposure was 8 hrs/day, 6 days/week, occupational exposure. Additional data are available from Ref. AD-13.

(b) Metabolite levels represent mean values obtained from sample urinalyses.

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	(human)	(10, 25, 50, 60, or 120 ppm, inhalation)(a)	(trichloroethanol)	681.8 mg/L (120 ppm exposure)	(urine)	(AD-13)
(a) exposure was 8 hrs/day, 6 days/ week, occupa- tional exposure. additional data are available from Ref. AD-13.			trichloroacetic acid	17.6 mg/L (10 ppm exposure)	urine	
				77.2 mg/L (25 ppm exposure)	urine	
				146.6 mg/L (50 ppm exposure)	urine	
				155.4 mg/L (60 ppm exposure)	urine	
				230.1 mg/L (120 ppm exposure)	urine	
	dog	dose and method not stated	trichloroethanol	15-20% of absorbed TCE (4 days)	urine	AD-14
			trichloroacetic acid	5-8% of absorbed TCE (4 days)	urine	
	rat	inhalation; dose not stated	trichloroacetic acid	4% of inhaled amount of TCE	urine	AD-14

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	rat	oral administration, dose not stated	trichloroethanol	15%	urine	AD-14
			trichloroacetic acid	3%	urine	
	rat	^{38}Cl-TCE, dose not stated, by gavage	trichloroethanol	10-15%	urine	AD 2 and
			trichloroacetic acid	1-5%	urine	AD-14
	calf	3 or 12 g, oral (daily, 4 or 5 days)	trichloroethylene	trace amounts	urine	AD-14 and AD-15
			trichloroethanol	13-25%	urine	
			trichloroacetic acid	1%	urine	
	human	1,042 ug/L air, inhalation (5 hrs)	trichloroethanol and trichloroacetic acid	8.4% (3rd day post-exposure)	feces	AD-10
			trichloroacetic acid	0.15-0.35 mg/100 ml (3rd day post-exposure)	sweat	
				0.10-0.15 mg/100 ml (3rd day post-exposure)	saliva	
			trichloroethanol	0.10-1.92 mg/100 ml (3rd day post-exposure)	sweat	
				0.09-0.32 mg/100 ml (3rd day post-exposure)	saliva	

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	human	50 ppm, inhalation (6 hrs/day, 5 days)	trichloroethanol	2.3 ug/mL	blood	AD-16
			trichloroacetic acid	50 ug/ml	blood	
	human	48 ppm, inhalation (4 hrs/day, 5 days)	trichloroethanol	1.28-2.85 ug/mL (1^{st} day of exposure)	blood	AD-17
				0.57-1.30 ug/ml (2^{nd} day)		
				2.01-2.53 ug/ml (3^{rd} day)		
				1.57-2.58 ug/ml (4^{th} day)		
				1.97-2.87 ug/ml (5^{th} day)		
				0.51-2.11 ug/ml (1^{st} day post-exposure)		
				0.18-0.51 ug/ml (2^{nd} day post-exposure)		

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	human	48 ppm, inhalation (4 hrs/day, 5 days	trichloroethanol	0.03-0.27 ug/ml (3^{rd} day post-exposure)	blood	AD-17
				0.03 ug/ml (7^{th} day post-exposure)	blood	
	human	40 or 44 ppm, inhalation (4 hrs)	trichloroethanol	0.706-1.776 ug/ml (at end of exposure)	blood	AD-17
				less than 0.03-0.123 ug/ml (96 hrs after start of exposure)		
	human	50 ppm, inhalation (6 hrs/day, 5 days)	trichloroethanol	2.0 ug/ml (maximum level attained)	blood	AD-18
	human	250 ppm (12 min/hr), inhalation (6 hr/day, 5 days)	trichloroethanol	2.5 ug/ml (maximum level attained)	blood	AD-18
	human	100 ppm (constant), inhalation (6 hr/day, 5 days)	trichloroethanol	5.0 ug/ml (maximum level attained)	blood	AD-18

Compound	Species	Rate and Route of administration	Metabolites			
			Compound	Percent of dose	Site	Ref.
Trichloroethylene (TCE) (continued)	human	1042 ug/L air, inhalation (5 hrs)	trichloroacetic acid	2.4 mg/100 ml (3^{rd} day post-exposure)	plasma	AD-10
				0.5 mg/100 ml of red cell mass (3^{rd} day post-exposure)	red blood cells	
(b) further information on the levels of TCE in fat and other tissues is given in Table 7 of Ref. AD-1.	guinea pig(b)	6-9 mg/L air, chronic inhalation (4-5 hrs/day, 5-23 days)	trichloroethylene	3.1-3.9 mg/100 g fresh tissue	fat	AD-1
			trichloroacetic acid	up to 4.4 mg/100 g fresh tissue	fat	

APPENDIX B

Summary Table

of

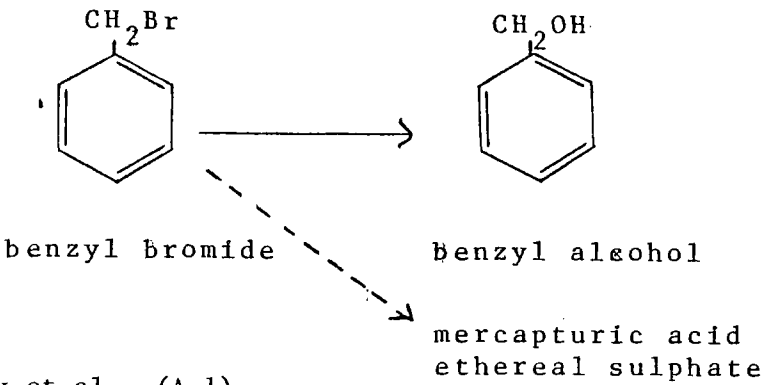
The Levels of Parent Halocarbon and Metabolites
Identified in Blood, Breath, and Urine

INTRODUCTION

After completion of the text and summary table (Appendix A) it was determined that the metabolism data could be presented in a more useful manner for those interested in exposure monitoring. Appendix B was designed as a reference table for this purpose. It includes the reported levels of 30 halogenated hydrocarbon compounds and their metabolites found in physiological media (i.e., blood, breath, and urine) that can be readily monitored. Wherever possible, a proposed metabolic pathway reported in the literature is presented along with the tabular data for each compound.

Since the data is taken from Appendix A, the reference numbers of Appendix B correspond to the original references found in Appendix A. Additional data and details of experimental methods may be obtained from the original references.

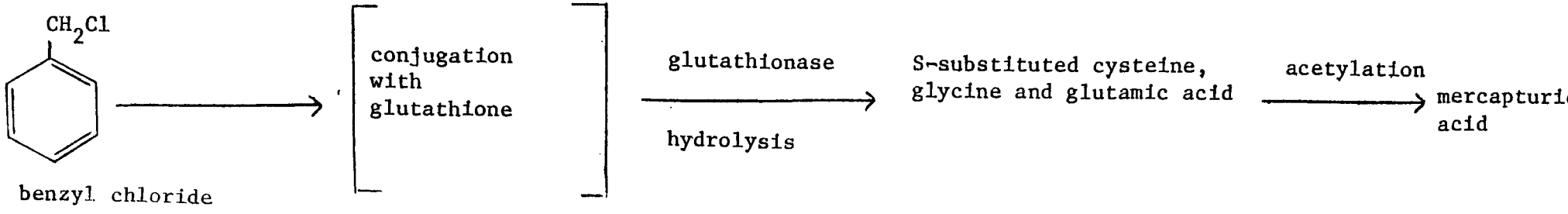
BENZYL BROMIDE



Based on findings of Bray et al., (A-1)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:	No data	No data	No data		
Half-life of metabolite:	No data	No data	No data		
Metabolite conjugates:					
mercapturic acid		19% (24 hrs)		rabbit, 0.2 g/kg, via stomach tube	A-1
ethereal sulphate		2% (24 hrs)		rabbit, 0.2 g/kg, via stomach tube	A-1

BENZYL CHLORIDE (CHLOROTOLUENE)



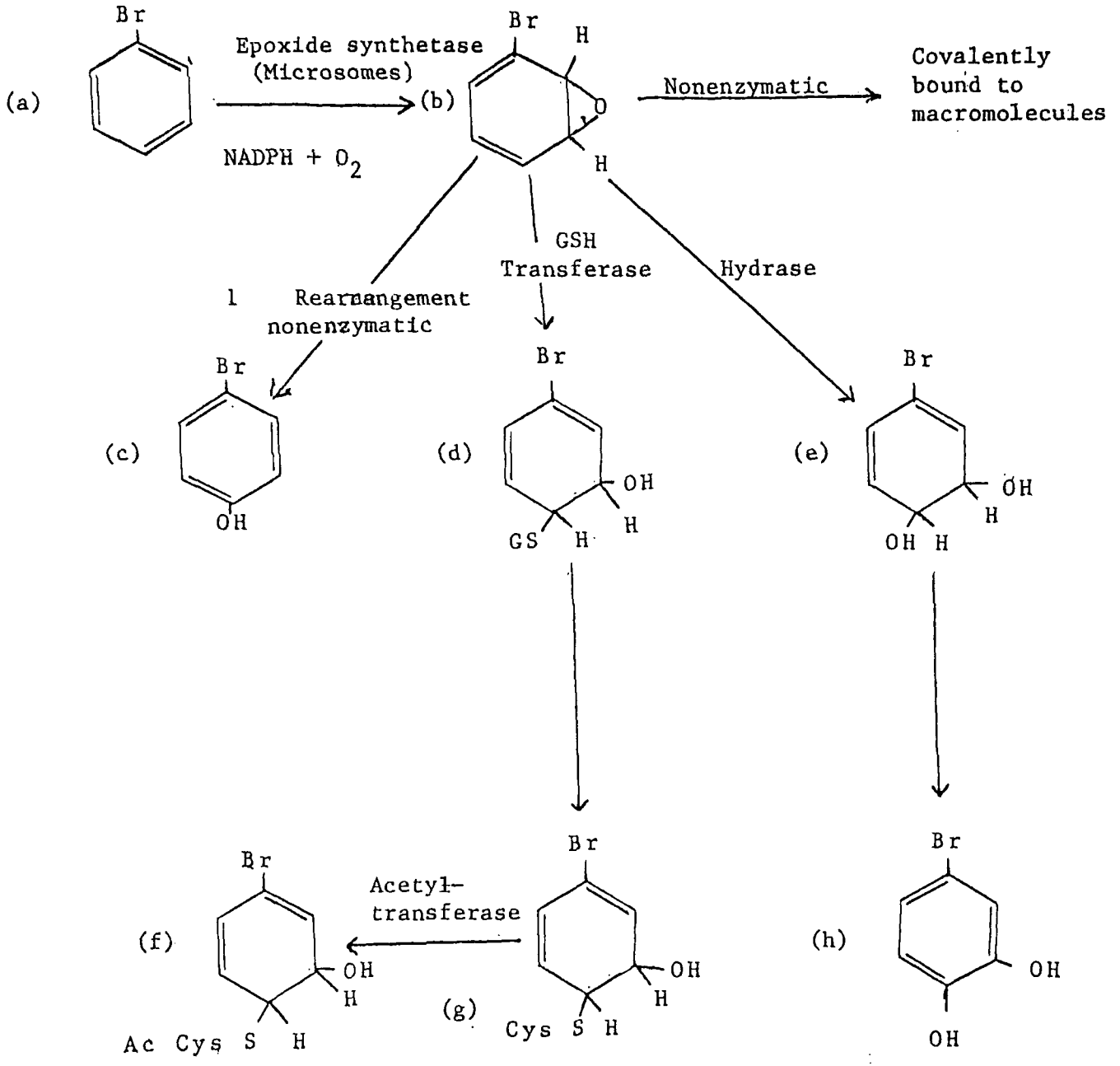
Proposed pathway for the formation of mercapturic acid Bray et al., (B-2)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
benzoic or phenyl-acetic acids (unconjugated)		17% (24 hrs)		rabbit, 0.2 g/kg, by stomach tube	B-1
Metabolite conjugates:					
mercapturic acid		49% (36-67%) (24 hrs)		rabbit, 0.2 g/kg, by stomach tube	B-1
		4%		guinea pig, rate and route unspecified	B-2
		27%		rat, rate and route unspecified	B-2

Benzyl chloride (Chlorotoluene)(continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates: (cont.)					
glycine conjugate (benzoic or phenylacetic)		20% (12-16) (24 hrs)		rabbit, 0.2 g/kg, by stomach tube	B-1
glucosiduronic acid (mainly phenols)		0.4% (0-5) 24 hrs		rabbit, 0.2 g/kg, by stomach tube	B-1

Proposed metabolic pathway (Jollow et al., 1974, Pharmacol. 11: 151-169)



(a) Bromobenzene
(b) Bromobenzene epoxide
(c) p-Bromophenol
(d) 3,4-Dihydro-3-hydroxy-4-S-glutathionyl bromobenzer
(e) 3,4-Dihydro-3,4-dihydroxy-bromobenzene
(f) 3,4-Dihydro-3-hydroxy-4-S-acetyl cysteinyl bromobenzen
(g) 3,4-Dihydro-3-hydroxy-4-S-cysteinyl bromobenzene
(h) 3,4-Dihydroxy bromobenzene

Bromobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	6% (1-2 days)			rabbit, 0.5 g/kg, oral dose	C-1
	6.3%			rabbit, 0.5 g/kg, stomach tube	C-2
Half-life of parent compound:	No data	No data	No data		
Metabolic half-life:				rat, 10 umol ^{14}C-bromobenzene, i.v.	C-6
9.8 min., whole body homogenate				rat, 10 umol ^{14}C-bromobenzene, i.v.	C-6
9.3 min., plasma				rat, 10 umol ^{14}C-bromobenzene, i.v.	C-6
9.5 min., liver				rat, 10 umol ^{14}C-bromobenzene, i.v.	C-6
Metabolites:					
monophenols (uncharacterized)		2-3% (1-2 days)		rabbit, 0.5 g/kg, oral dose	C-1
4-bromophenol		40% (48 hrs)		rat, dosage not stated, i.p. injection	C-7
		37% (48 hrs)		rat, 10.0 mmol/kg, i.p. injection	C-6
		18% (48 hrs)		rat, 0.05 mmol/kg, i.v. injection	C-6
		1.2% (a) (10 days)		rabbit, 50 mg/kg, i.p. injection	C-5
3-bromophenol		1.0% (a) (10 days)		rabbit, 50 mg/kg, i.p. injection	C-5

(a) figure shown is percent yield of metabolite obtained by extraction and purification of the ether extracts of hydrolyzed rabbit urine

Bromobenzene (continued)

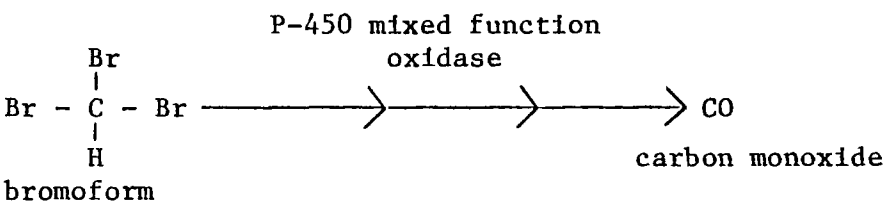
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
2-bromophenol		4% (48 hrs)		rat, dosage not stated, i.p. injection	C-7
		3% (48 hrs)		rat, 0.05 mmol/kg, i.v. injection	C-6
		3% (48 hrs)		rat, 10.0 mmol/kg, i.p. injection	C-6
bromophenyldihydrodiol		4% (48 hrs)		rat, 10.0 mmol/kg, i.p. injection	C-6
		4% (48 hrs)		rat, 0.05 mmol/kg, i.v. injection	C-6
3-4-bromophenyldihydrodiol		3% (48 hrs)		rat, dosage not stated, i.p. injection	C-7
2-3-bromophenyldihydrodiol		trace (48 hrs)		rat, dosage not stated, i.p. injection	C-7
bromocatechols (uncharacterized)		28% (1-2 days)		rabbit, 0.5 g/kg, oral dose	C-1
		6% (48 hrs)		rat, 10.0 mmol/kg, i.p. injection	C-6
		4% (48 hrs)		rat, 0.05 mmol/kg, i.v. injection	C-6

Bromobenzene (continued)

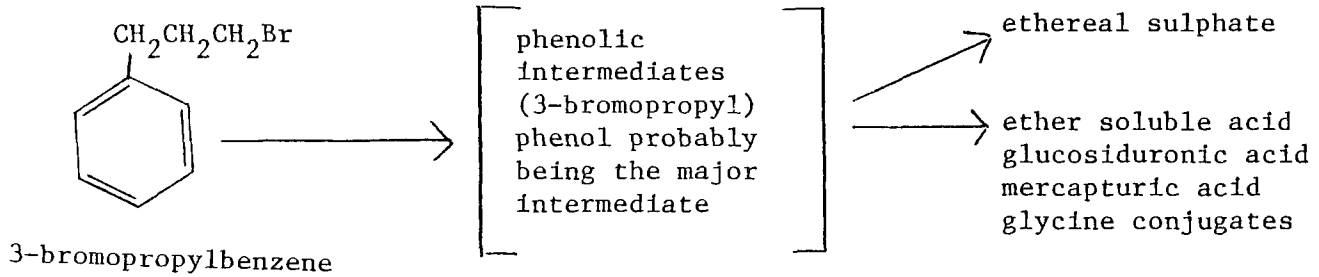
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
3,4-bromocatechol		4% (48 hrs)		rat, dosage not stated, i.p. injection	C-7
2,3-bromocatechol		trace (48 hrs)		rat, dosage not stated, i.p. injection	C-7
Metabolite conjugates:					
total o-conjugates		58% (1-2 days)		rabbit, 0.5 g/kg, oral dose	C-1
total conjugates		97.9%		rabbit, 210 mg/kg, via stomach tube	C-3
glucuronide		40.2%		rabbit, 210 mg/kg, via stomach tube	C-3
ethereal sulphate		36.8%		rabbit, 210 mg/kg, via stomach tube	C-3
mercapturic acid		20.9%		rabbit, 210 mg/kg, via stomach tube	C-3
		25% (1-2 days)		rabbit, 0.5 g/kg, oral dose	C-1
bromophenylmercapturic acid		70% (48 hrs)		rat, 0.05 mmol/kg, i.v. injection	C-6
		48% (48 hrs)		rat, 10.0 mmol/kg, i.v. injection	C-6
		22%		rabbit, 0.5 mg/kg, via stomach tube	C-4

BROMOFORM

No data were available regarding bromoform metabolites in breath, urine or blood. The following metabolic scheme represents the reduction of bromoform to carbon monoxide, based on in vitro studies (D-1).



3-BROMOPROPYLBENZENE



3-bromopropylbenzene

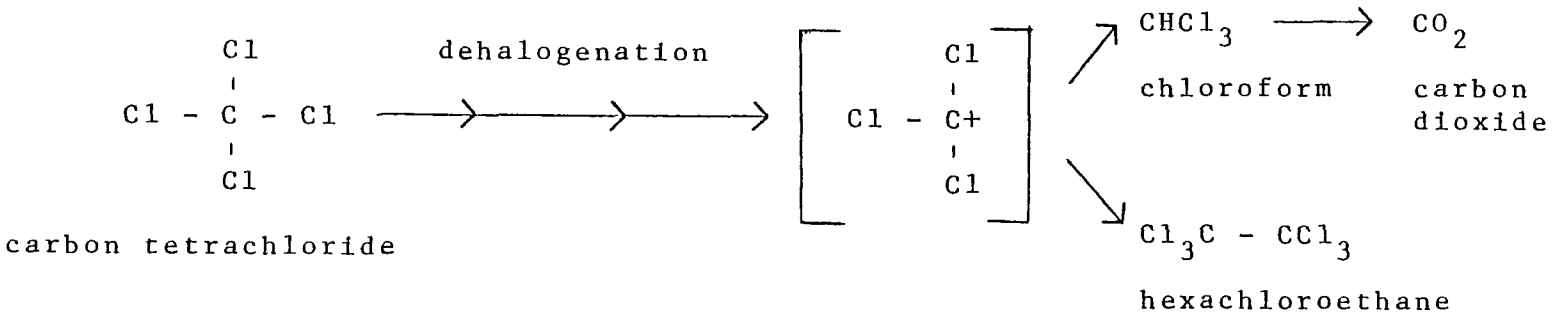
Based on findings reported by Bray et al., (E-1)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
total urinary metabolites		89%		rabbit, 0.25 g/kg, via stomach tube	E-1

3-Bromopropylbenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates:					
ethereal sulphate		20%		rabbit, 0.25 g/kg, via stomach tube	E-1
ether soluble acid (primarily glucosiduronic acid; also mercapturic acid and glycine conjugates)		69%		rabbit, 0.25 g/kg, via stomach tube	E-1
phenaceturic acid		unspecified amount		rabbit, 0.25 g/kg, via stomach tube	E-1
N-acetyl-S-(3-phenyl - propyl)-L-cysteine		unspecified amount		rabbit, 0.25 g/kg, via stomach tube	E-1
phenolics (uncharacterized)		unspecified amount		rabbit, 0.25 g/kg, via stomach tube	E-1

CARBON TETRACHLORIDE



Based on findings of Paul and Rubinsteins, (F-2)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	33% (1 hr)			human, 80 ppm ^{14}carbon tetrachloride, single breath inhalation	F-3
	40% (1800 hrs)			monkey, 46 ppm ^{14}carbon tetrachloride, inhalation for 344 minutes	F-4
	85% (18 hrs)			rat, 1.0 ml ^{14}carbon tetrachloride /kg, intraduodenal	F-2
		19.2 ug total (day 1)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		5.9 ug total (day 2)		sheep, 0.1 mg/kg, intra-ruminal	F-6

Carbon tetrachloride (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
		4.6 ug total (day 3)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		trace-1.3 ug (day 4-7)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		1.2 ug total (day 1)		sheep, 0.12 mg/kg, intra-ruminal	F-6
		1.0 ug total (day 2)		sheep, 0.12 mg/kg, intra-ruminal	F-6
		0.7 ug total (day 3)		sheep, 0.12 mg/kg, intra-ruminal	F-6
		trace-0.7 ug (day 4-7)		sheep, 0.12 mg/kg, intra-ruminal	F-6
			trace (at end of exposure)	rabbit, 110 ppm, inhalation, 4 hrs	F-7
			0.2 mg/100 ml blood (at end of exposure)	rabbit, 225 ppm, inhalation, 4 hrs	F-7
			0.6 mg/100 ml blood (at end of exposure)	rabbit, 345 ppm, inhalation, 4 hrs	F-7
			0.4 mg/100 ml blood (at end of exposure)	rabbit, 600 ppm, inhalation, 4 hrs	F-7
Half-life of parent compound:	No data	No data	No data		

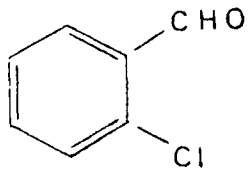
Carbon tetrachloride (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites:					
^{14}C-carbon dioxide	11% (1800 hrs)			monkey, 46 ppm ^{14}carbon tetrachloride, inhalation, 344 minutes	F-4
	1% (18 hrs)			rat, 1.0 ml ^{14}carbon tetrachloride/kg, intraduodenal	F-2
chloroform		3.7 ug total (day 1)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		2.0 ug total (day 2)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		1.8 ug total (day 3)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		trace-0.8 ug (day 4-7)		sheep, 0.1 mg/kg, intra-ruminal	F-6
		6.6 ug total (day 1)		sheep, 0.12 mg/kg, intra-ruminal	F-6
		1.0 ug total (day 2)		sheep, 0.12 mg/kg, intra-ruminal	F-6
		0.7 ug total (day 3)		sheep, 0.12 mg/kg, intra-ruminal	F-6
		trace-0.7 ug total (day 4-7)		sheep, 0.12 mg/kg, intra-ruminal	F-6

Carbon tetrachloride (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates:	No data	No data	No data		

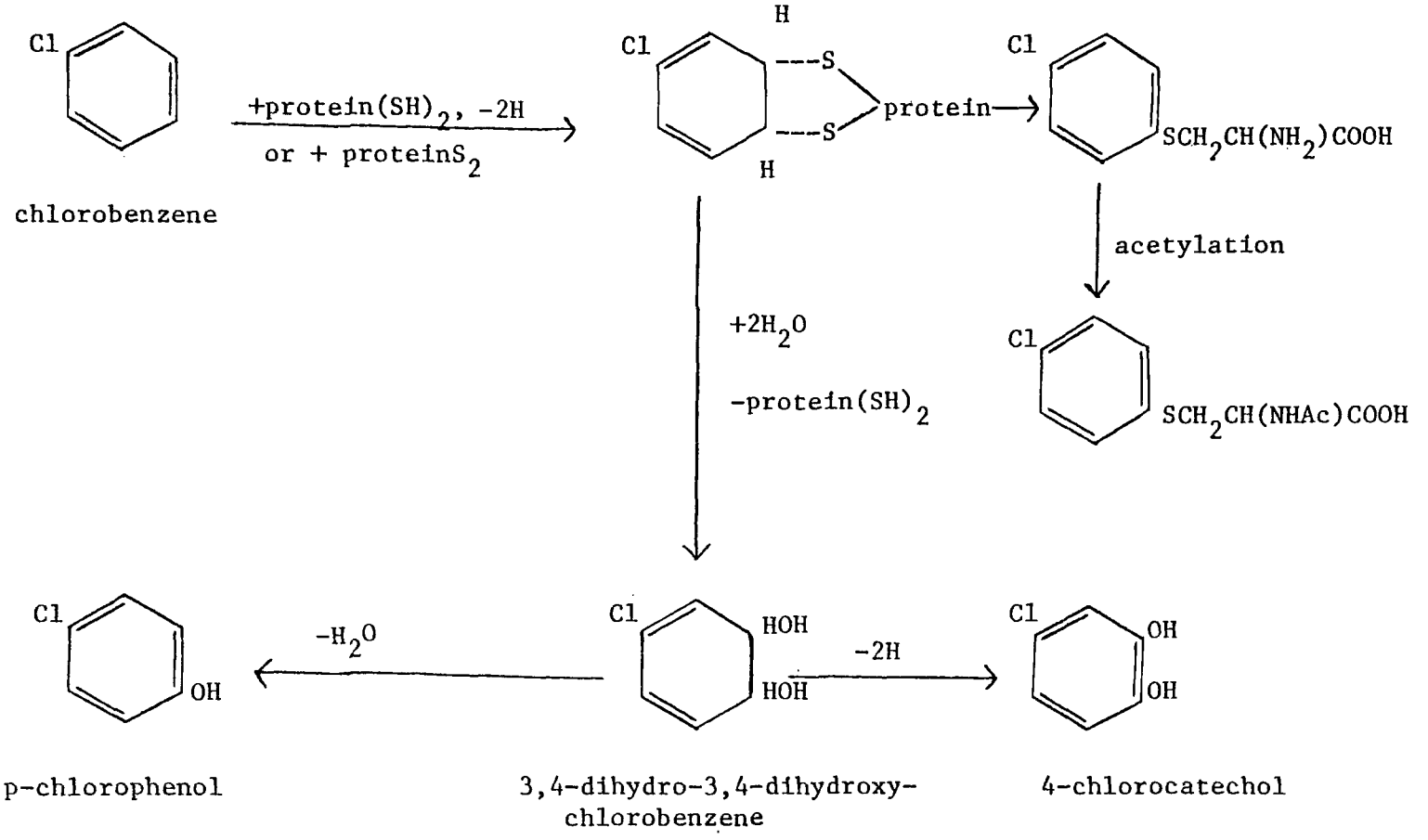
o-CHLOROBENZALDEHYDE



o-chlorobenzaldehyde

	Breath	Urine	Blood	Comments	Ref.
Parent Compound:	No data	No data	No data		
Half-life of parent compound:			15 seconds	human, 2.65 uM, in vitro blood tests	G-1
			70 seconds	cat, 2.65 uM, in vitro blood tests	G-1
			15 seconds	rat, 2.65 uM, in vitro blood tests	G-1
Metabolites:	No data	No data	No data		
Metabolite conjugates:	No data	No data	No data		

CHLOROBENZENE



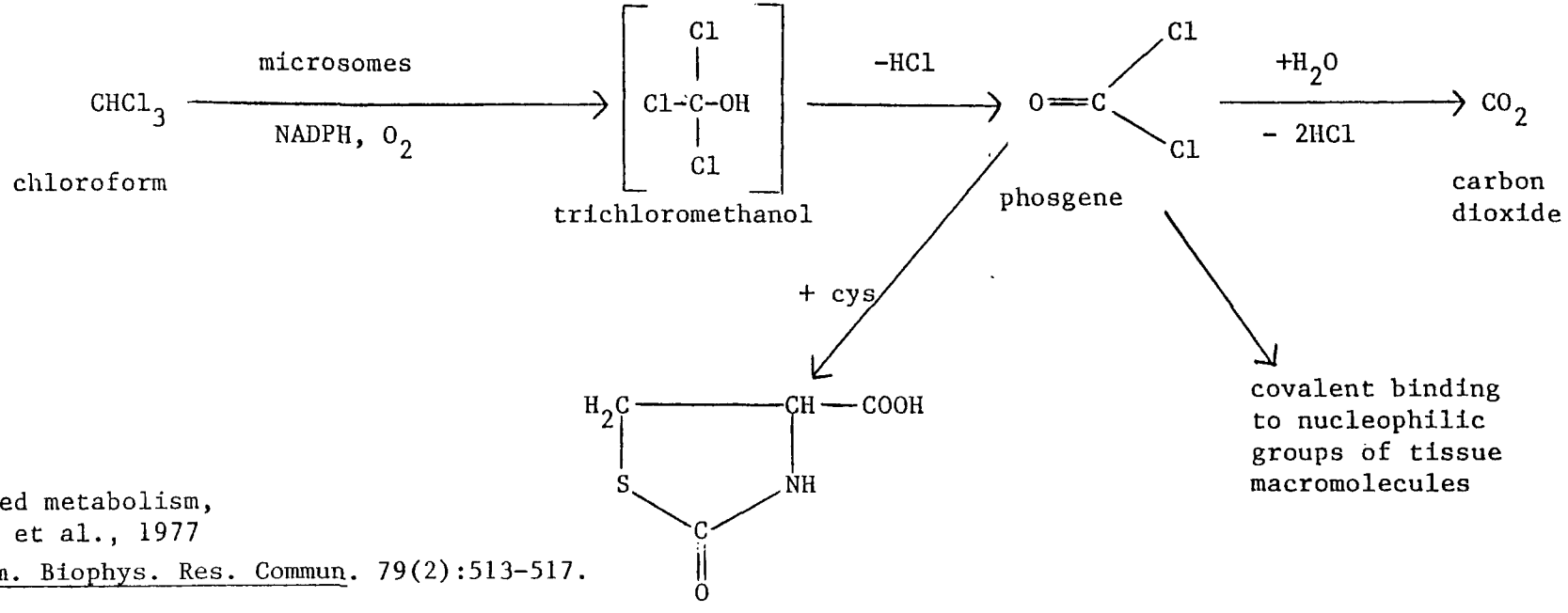
Proposed by Smith et al., 1950 (H-2)

Chlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	27%			rabbit, 0.5 g/kg, oral	H-3
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
^{14}C-activity		19.6%		rabbit, 0.5 g ^{14}C-chlorobenzene, orally, twice daily for 4 days	H-5
total urinary metabolites		72.2%		rabbit, 150 mg/kg, via stomach tube	H-1
glucuronide		25.2%		rabbit, 150 mg/kg, via stomach tube	H-1
(a) expressed as percentage of urinary ^{14}C-activity (19.6% of total ^{14}C-chlorobenzene dose)		33.57%(a)		rabbit, 0.5 g ^{14}C-chlorobenzene, orally twice daily for 4 days	H-5
ethereal sulphate		26.6%		rabbit, 150 mg/kg, via stomach tube	H-1
		33.88%(a)		rabbit, 0.5 g ^{14}C-chlorobenzene, orally, twice daily for 4 days	H-5
mercapturic acid		20.4%		rabbit, 150 mg/kg, via stomach tube	H-1
		23.80%(a)		rabbit, 0.5 g ^{14}C-chlorobenzene, orally, twice daily for 4 days	H-5
		28%		rabbit, 0.5 g/kg, oral	H-3
		27%		rabbit, 0.5 g/kg, oral	H-4
p-chlorophenylmercapturic acid		major metabolite (2 days)		rabbit, 10 or 12 g total dose, via stomach tube	H-2
catechols		27%		rabbit, 0.5 g/kg, oral	H-4

Chlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
catechol derivatives (uncharacterized)		37%		rabbit, 0.5 g/kg, oral	H-3
4-chlorocatechol (ethereal sulphate and glucuronide conjugates)		major metabolite (2 days)		rabbit, 10 or 12 g total dose, via stomach tube	H-2
monophenols (uncharacterized)		2.84%(a)		rabbit, 0.5 g ^{14}C-chlorobenzene, orally, twice daily for 4 days	H-5
p-chlorophenol		2-3%		rabbit, 0.5 g/kg, oral	H-3
o-chlorophenol		trace		rabbit, 0.5 g/kg, oral	H-3
p-chlorophenol and p-chlorophenol glucuronide		0.5% (2 days)		rabbit, 10 or 12 g total dose, via stomach tube	H-2
diphenols		4.17%(a)		rabbit, 0.5 g ^{14}C-chlorobenzene, orally, twice daily for 4 days	H-5
3,4-dihydro-3,4-dihychoxychlorobenzene		0.57%(a)		rabbit, 0.5 g ^{14}C-chlorobenzene, orally, twice daily for 4 days	H-5
		0.03% (2 days)		rabbit, 10 or 12 g total dose, via stomach tube	H-2



Proposed metabolism,
Mansuy et al., 1977
Biochem. Biophys. Res. Commun. 79(2):513-517.

4-carboxy-thiazolidine-2-one.

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	17.8-66.6% (8 hrs)			human, 4 males, 500 mg, oral	I-3

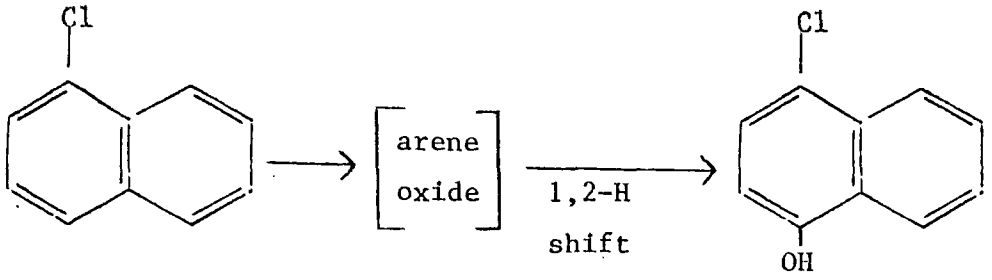
Chloroform (continued)

	Breath	Urine	Blood	Comments	Ref.
arent compound (cont.)					
	25.6-40.4% (8 hrs)			human, 4 females, 500 mg, oral	I-3
	10%			human, 5 mg single breath inhalation	I-4
	78%			monkey, 60 mg/kg, oral dose daily for 5 days	I-2
	20%			rat, 60 mg/kg, oral dose daily for 5 days	I-2
(a) chloroform combined with toluene-soluble metabolites	20%(a) (24 hrs)			rat, 60 mg/kg, oral	I-1
	6%			mouse, 60 mg/kg, oral dose, daily for 5 days	I-2
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
carbon dioxide	50.6% (8 hrs)			human, 4 males, 500 mg, oral	I-3
	48.5% (8 hrs)			human, 4 females, 500 mg, oral	I-3
	18% (24 hrs)			monkey, 60 mg/kg, oral	I-1
	16%			monkey, 60 mg/kg, oral dose, daily for 5 days	I-2
Metabolite conjugates:	No data	No data	No data		

Chloroform (continued)

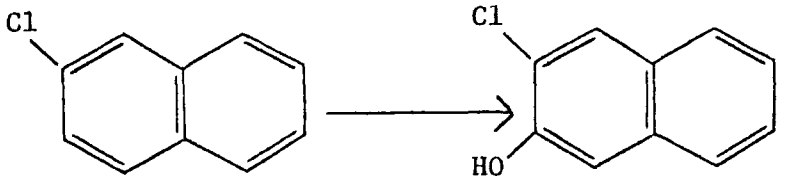
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
	66% (24 hrs)			rat, 60 mg/kg, oral dose, daily for 5 days	I-2
	80% (24 hrs)			mouse, 60 mg/kg, oral	I-1
bicarbonate/carbonate compounds	13% (24 hrs)			mouse, 60 mg/kg, oral	I-1

Based on findings of Ruzo et al. 1976. J. Agr Chem and Food 24(3): 581-3.



1-chloronaphthalene

4-chloro-1-naphthol



2-chloronaphthalene

3-chloro-2-napthol

	Breath	Urine	Blood	Comments	Ref.
Parent compound: 1-Cl naphthalene			5.1 ug/g after 10 min. 3.4 ug/g after 20 min. 1.8 ug/g after 40 min. 0.7 ug/g after 80 min. 0.9 ug/g after 120 min. 0.3 ug/g after 160 min. 0.3 ug/g after 200 min. 0.1 ug/g after 240 min.	pig, 300 mg dose of 1-chloronaphthalene, 7.5 kg pig, retrocarotid administration	J-2

Chloronaphthalene (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
2-Cl naphthalene			6.2 ug/g after 10 min.	pig, 300 mg dose of 2-chloronaphthalene, 7.5 kg pig, retrocarotial administration	J-2
			3.8 ug/g after 20 min.		
			1.9 ug/g after 40 min.		
			1.0 ug/g after 80 min.		
			1.0 ug/g after 120 min.		
			0.6 ug/g after 160 min.		
			0.2 ug/g after 200 min.		
			0.2 ug/g after 240 min.		
			0.1 ug/g after 260 min.		
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
4-Cl naphthol		400 ug/g (6 hrs after administration)		Yorkshire pig, 300 mg of 1-Cl naphthalene isomer, 7.5 kg pig, retrocarotid administration	J-2

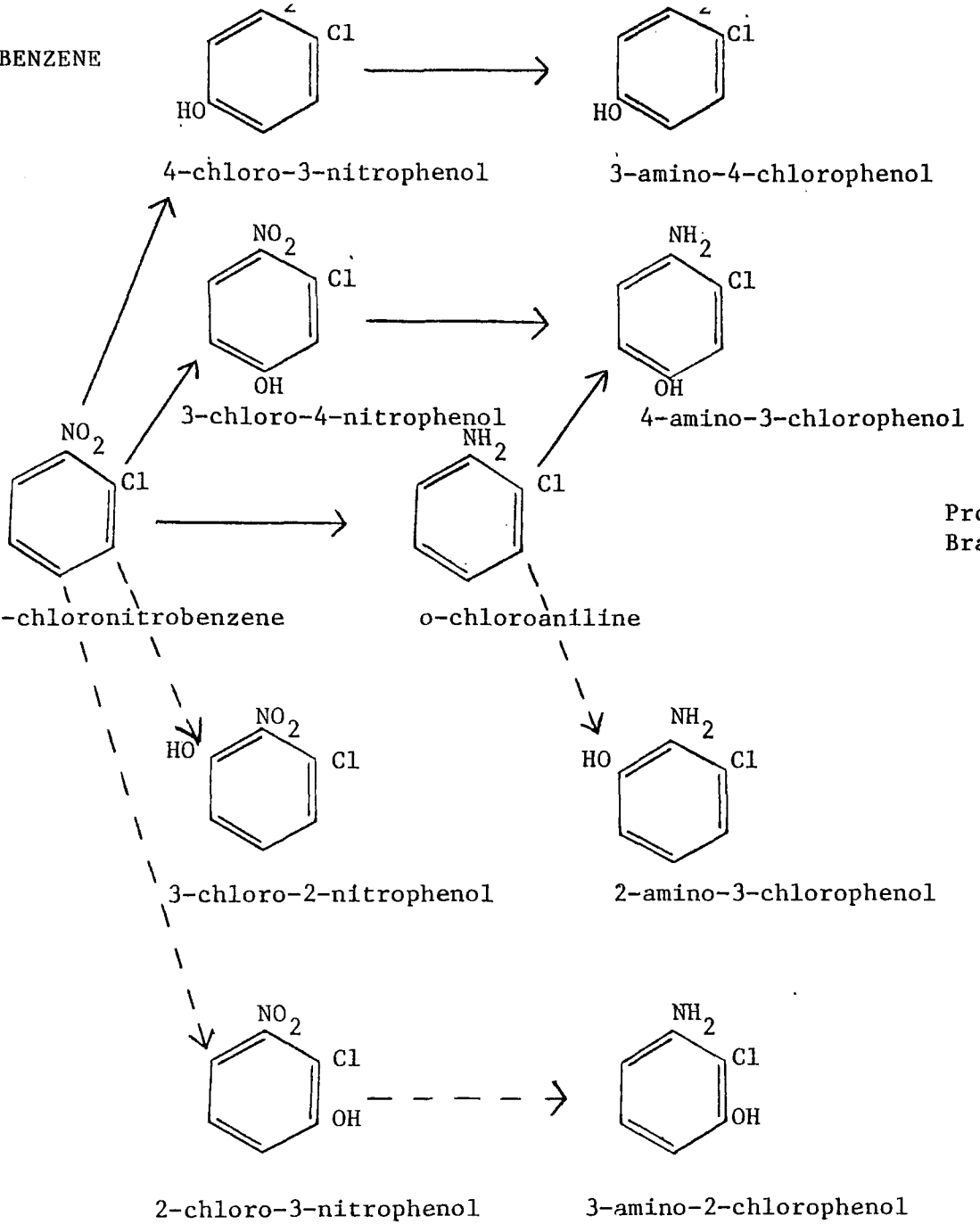
Chloronaphthalene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
4-Cl naphthol			0.1 ug/g after 160 min.		
			0.6 ug/g after 200 min.	Yorkshire pig, 300 mg of 1-Cl naphthalene isomer, 7.5 kg pig, retrocarotid administration	(J-2)
			0.8 ug/g after 240 min.		
			1.0 ug/g after 260 min.		
			1.3 ug/g after 300 min.		
free phenolic compounds		2% (4 days)		male albino rabbit, 1 g per rabbit, by stomach tube	J-1
3-Cl-2-naphthal		60 ug/g (6 hrs after administration)		Yorkshire pig, 300 mg of 2-Cl naphthalene isomer, 7.5 kg pig, retrocarotid administration	J-2
			0.2 ug/g after 200 min.		
			0.5 ug/g after 240 min.		
			0.8 ug/g after 260 min.		
			1.0 ug/g after 300 min.		

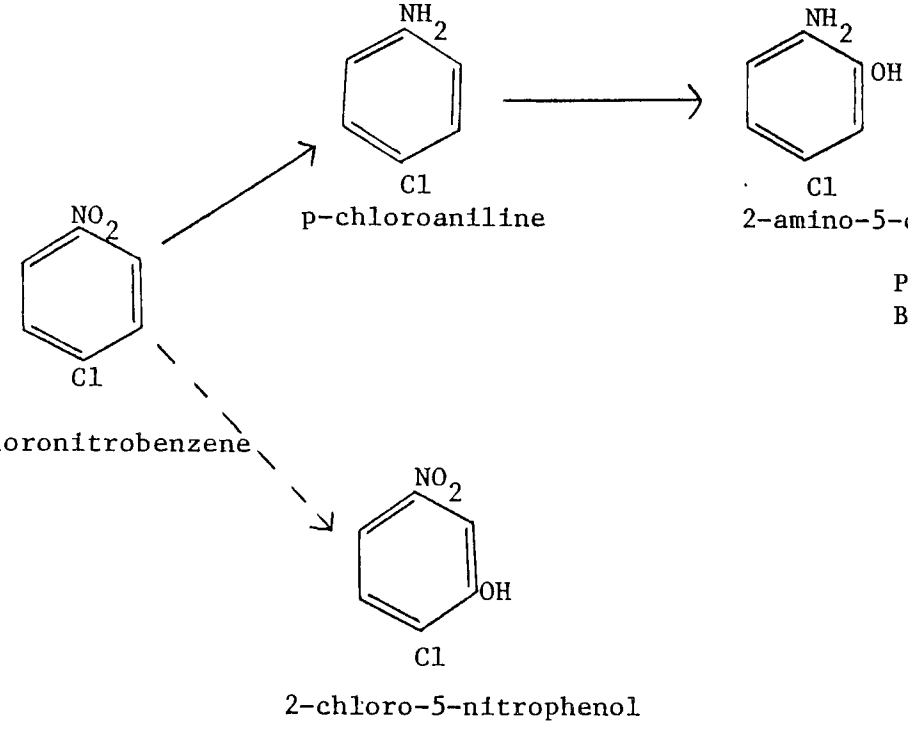
Chloronaphthalene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates of 1-chloronaphthlene:					
ethereal sulfate		10.1% (4 days)		male albino rabbits, 1 g/rabbit, by stomach tube. The rabbits weighed approximately 2 kg. Expressed as percentage of original dose	J-1
mercapturic acids		13.1% (4 days)			
glucuronic acid		53.7% (4 days)			

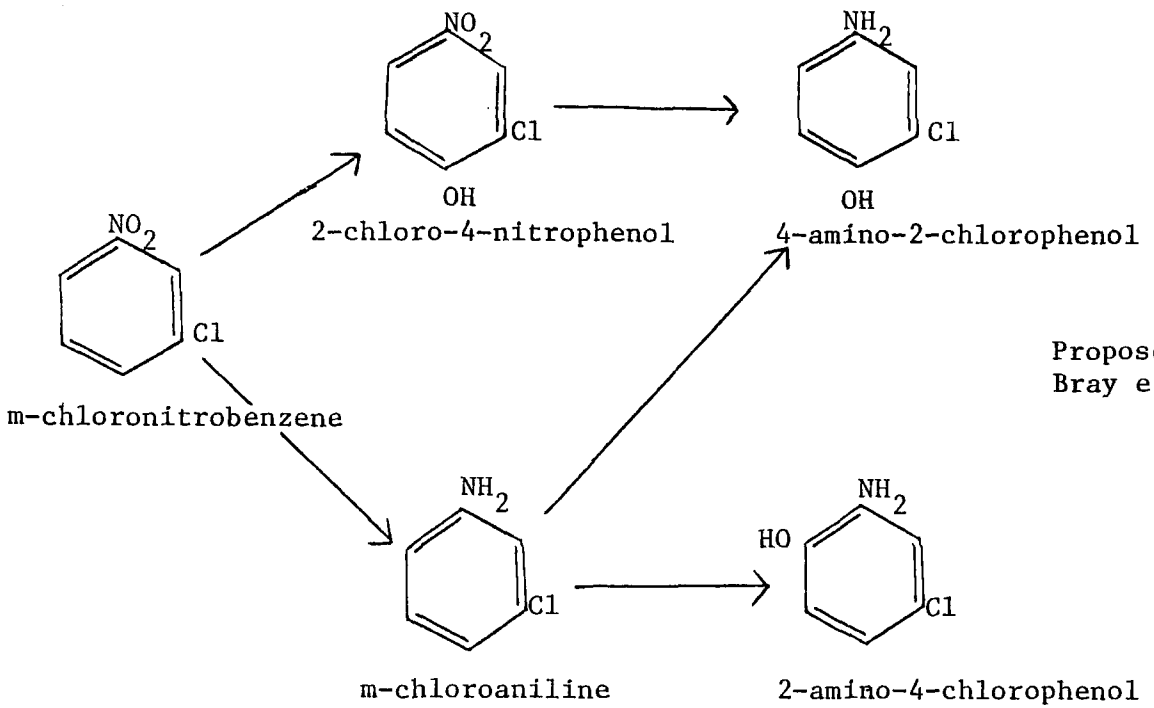
CHLORONITROBENZENE



Proposed metabolism of o-chloronitrobenzene, Bray et al., 1956 (K-1)



Proposed metabolism of p-chloronitrobenzene, Bray et al., 1956 (K-1)



Proposed metabolism of m-chloronitrobenzene, Bray et al., 1956 (K-1)

Chloronitrobenzene (continued)

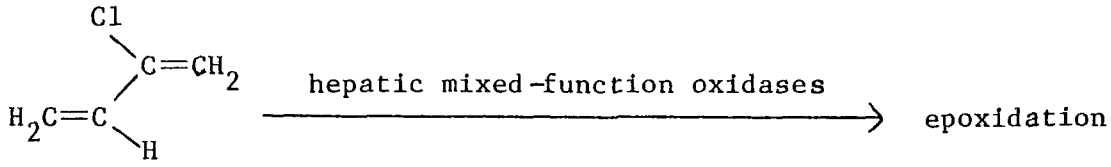
	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	Not detected	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites of o-chloronitrobenzene isomer:					
free chloroaniline		9%		rabbit, 0.1 g/kg. Expressed as percent of dose.	K-1
free phenolics		trace amounts		rabbit, 0.1 g/kg. Expressed as percent of dose.	K-1
Metabolites of m-chloronitrobenzene isomer:					
free chloroaniline		11%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
free phenolics		trace amounts		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
Metabolites of p-chloronitrobenzene isomer:					
free chloroaniline		9%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
free phenolics		trace amounts		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1

Chloronitrobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
etabolite conjugates of o-chloronitrobenzene isomer:					
ether glucuronide		42%		rabbit, 0.1 g/kg. Expressed as percent of dose.	K-1
ethereal sulphates (aminochlorophenols and chloronitrophenols)		24%		rabbit, 0.1 g/kg. Expressed as percent of dose.	K-1
nitrophenylmercapturic acid		7%		rabbit, 0.1 g/kg. Expressed as percent of dose.	K-1
Metabolite conjugates of m-chloronitrobenzene isomer:					
ether glucuronide		33%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
ethereal sulphates (aminochlorophenols and chloronitrophenols)		18%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
nitrophenylmercapturic acid		1%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
Metabolite conjugates of p-chloronitrobenzene isomer:					
ether glucuronide		19%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
ethereal sulphate (aminochlorophenols and chloronitrophenols)		21%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1

Chloronitrobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates of p-chloronitrobenzene isomer (cont.)					
conjugated chloroaniline		4%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
nitrophenylmercapturic acid (colorimetic method)		7%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1
nitrophenylmercapturic acid (modified Stekol method)		3%		rabbit, 0.2 g/kg. Expressed as percent of dose.	K-1

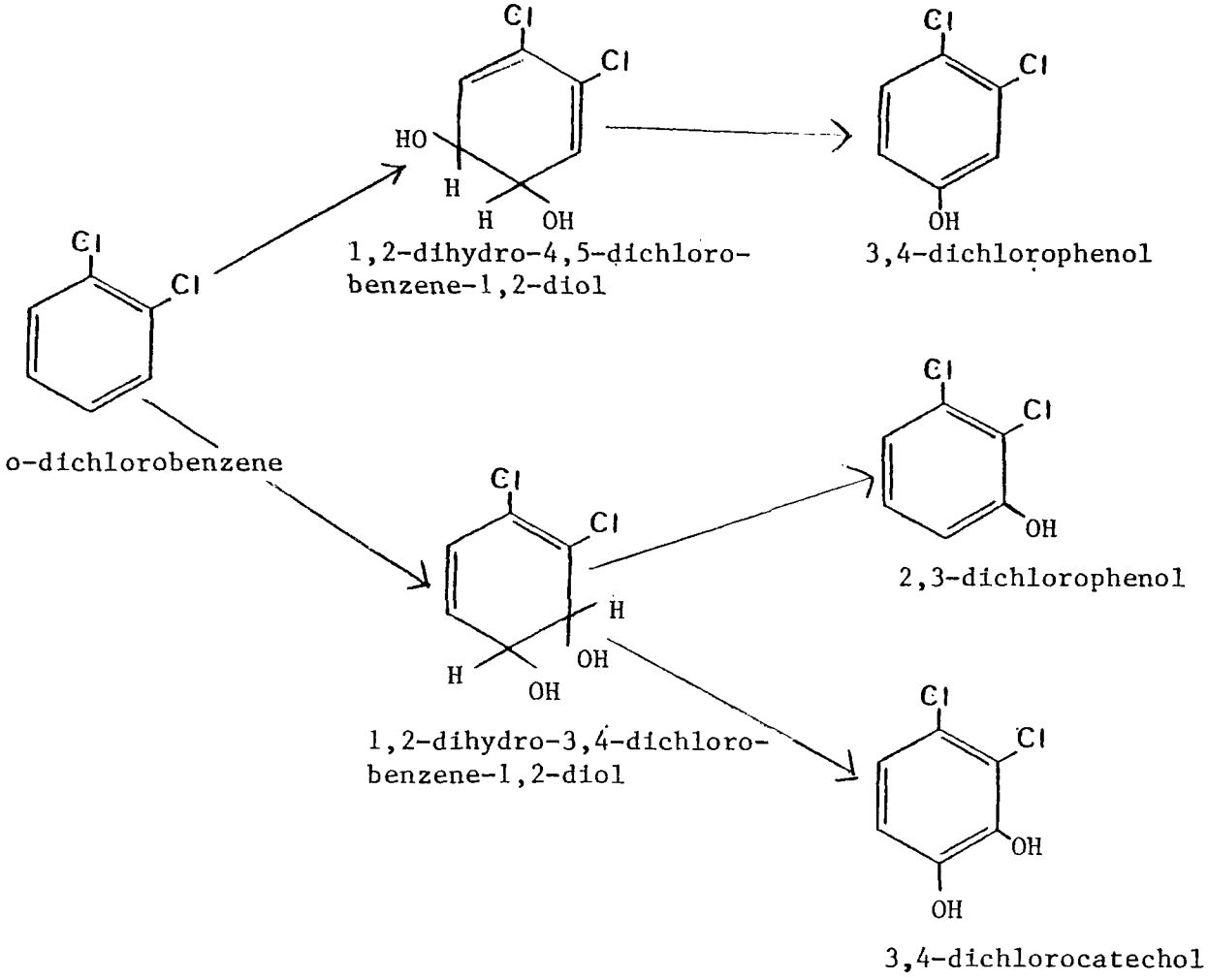


chloroprene

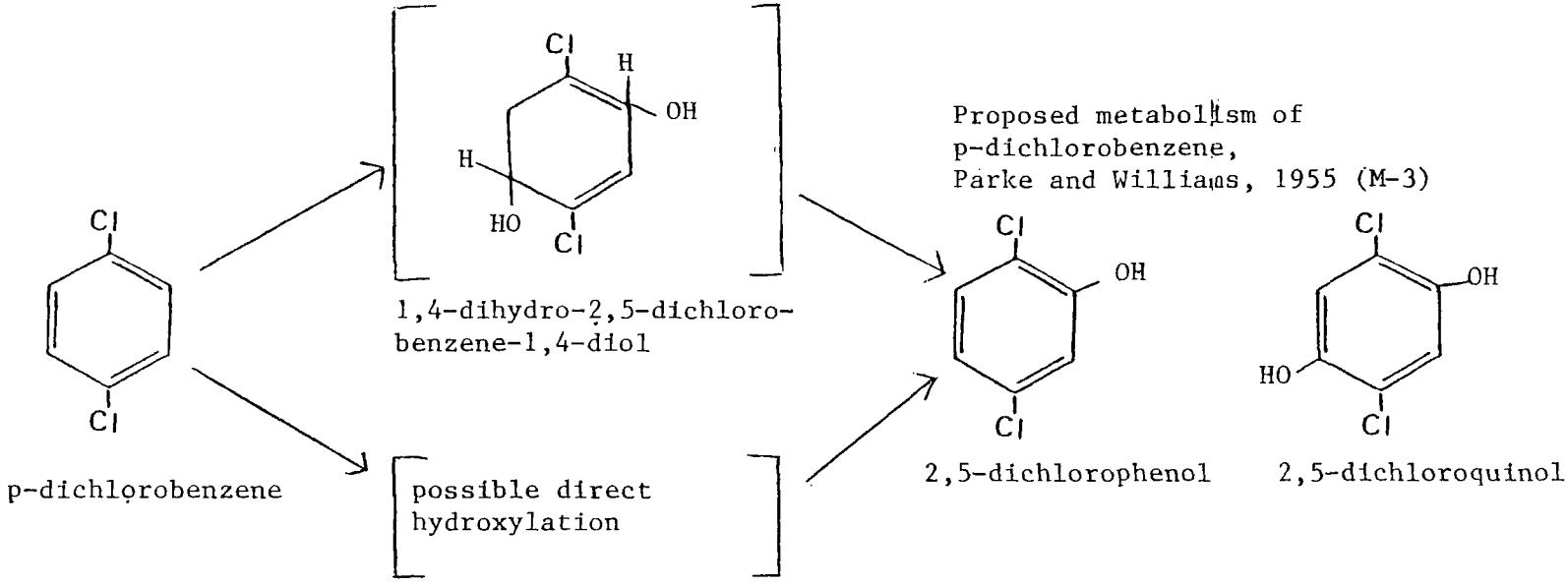
Based on findings of Bardodej, (L-1)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:	No data	No data	No data		
Metabolite conjugates:	No data	No data	No data		

CHLOROTOLUENE - SEE BENZYL CHLORIDE p. 187



Proposed metabolism of o-dichlorobenzene, Parke and Williams, 1955 (M-3)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1,4-dihydro-2,5-dichloro-
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Proposed metabolism of
p-dichlorobenzene,
Parke and Williams, 1955 (M-3)
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Cl
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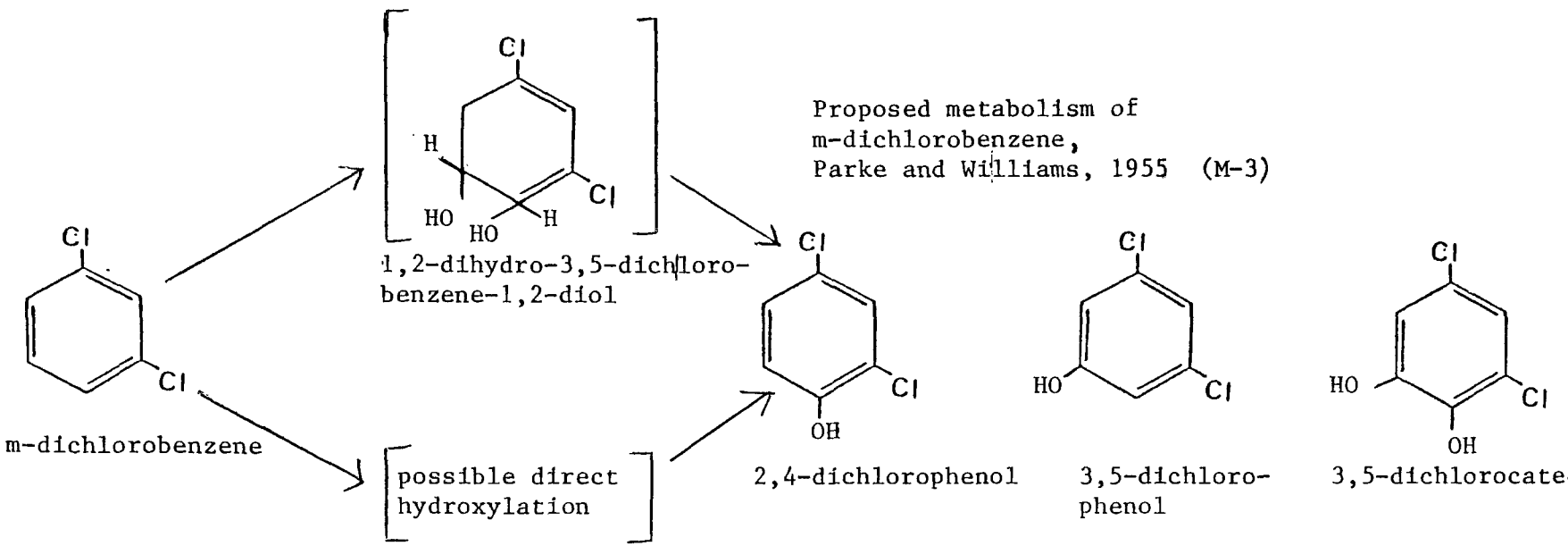
OH
HO
Cl
p-dichlorobenzene
possible direct
hydroxylation
2,5-dichlorophenol
2,5-dichloroquinol



Proposed metabolism of m-dichlorobenzene, Parke and Williams, 1955 (M-3)

Dichlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites of o-isomer:					
dichlorocatechol		7.8%		rabbit, 0.5 g/kg, via stomach tube	M-1
catechols		4%		rabbit, 0.5 g/kg, via stomach tube	M-2
		4%		rabbit, 0.5 g/kg, via stomach tube	M-3
quinols		0%		rabbit, 0.5 g/kg, via stomach tube	M-3
monophenols		39%		rabbit, 0.5 g/kg, via stomach tube	M-3
Metabolites of m-isomer:					
catechols		4%		rabbit, 0.5 g/kg, via stomach tube	M-2
		3%		rabbit, 0.5 g/kg, via stomach tube	M-3
quinols		0%		rabbit, 0.5 g/kg, via stomach tube	M-3
monophenols		25%		rabbit, 0.5 g/kg, via stomach tube	M-3
Metabolites of p-isomer:					
catechols		0%		rabbit, 0.5 g/kg, via stomach tube	M-2
		0%		rabbit, 0.5 g/kg, via stomach tube	M-3
quinols		6%		rabbit, 0.5 g/kg, via stomach tube	M-3
monophenols		35%		rabbit, 0.5 g/kg, via stomach tube	M-3

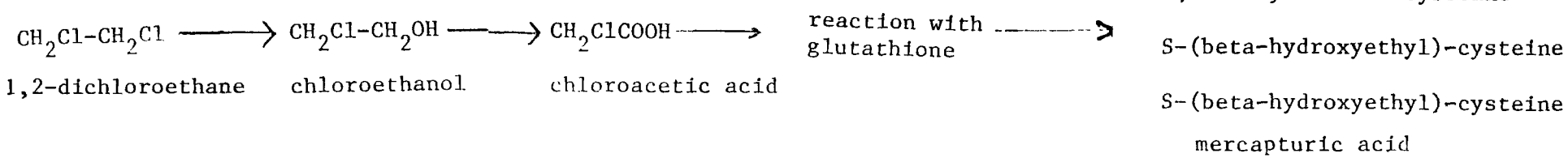
Dichlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates of o-isomer:					
glucuronides		48%		rabbit, 0.5 g/kg, via stomach tube	M-2
		48%		rabbit, 0.5 g/kg, via stomach tube	M-3
ethereal sulfates		21%		rabbit, 0.5 g/kg, via stomach tube	M-2
		21%		rabbit, 0.5 g/kg, via stomach tube	M-3
mercapturic acid		5%		rabbit, 0.5 g/kg, via stomach tube	M-2
		5%		rabbit, 0.5 g/kg, via stomach tube	M-3
Metabolite conjugates of m-isomer:					
glucuronides		31%		rabbit, 0.5 g/kg, via stomach tube	M-2
		36%		rabbit, 0.5 g/kg, via stomach tube	M-3
ethereal sulfates		11%		rabbit, 0.5 g/kg, via stomach tube	M-2
		7%		rabbit, 0.5 g/kg, via stomach tube	M-3
mercapturic acid		9%		rabbit, 0.5 g/kg, via stomach tube	M-2
		11%		rabbit, 0.5 g/kg, via stomach tube	M-3
Metabolite conjugates of p-isomer:					
glucuronides		37%		rabbit, 0.5 g/kg, via stomach tube	M-2

Dichlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates of p-isomer (cont.) (glucuronides, cont.)					
		36%		rabbit, 0.5 g/kg, via stomach tube	M-3
ethereal sulfate		27%		rabbit, 0.5 g/kg, via stomach tube	M-2
		27%		rabbit, 0.5 g/kg, via stomach tube	M-3
mercapturic acid		0%		rabbit, 0.5 g/kg, via stomach tube	M-2
		0%		rabbit, 0.5 g/kg, via stomach tube	M-3

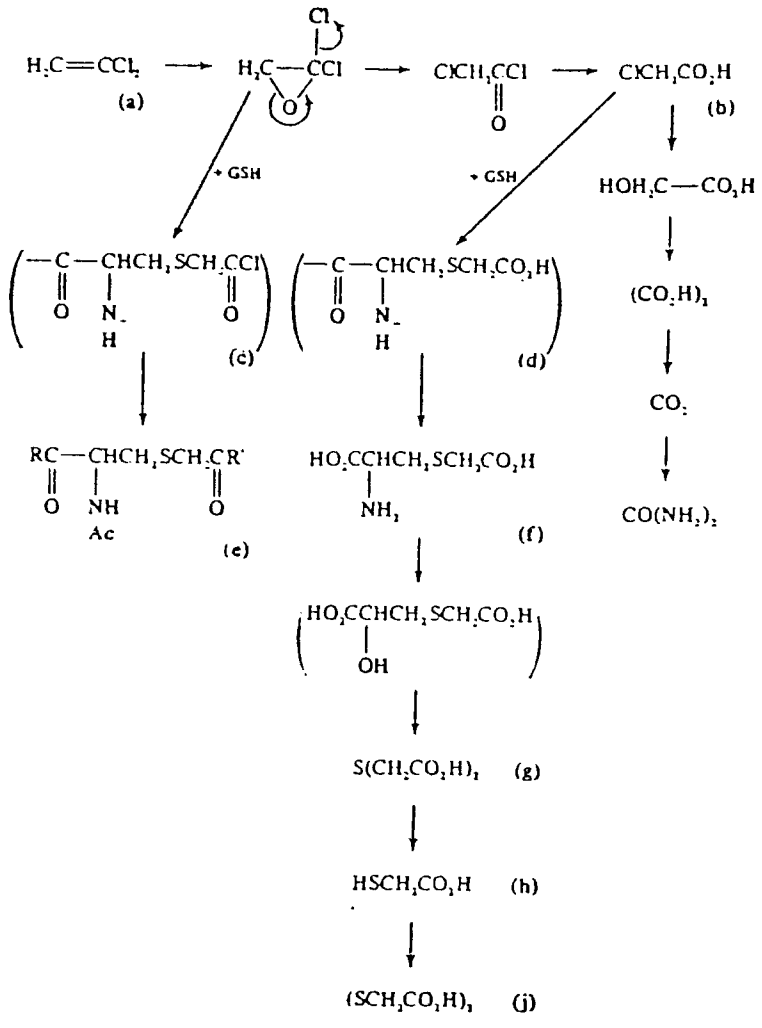
Proposed metabolic pathway of 1,2-dichloroethane, Yllner, 1979 (N-1)



	Breath	Urine	Blood	Comments	Ref.
Parent compound:					
^{14}C-1,2-dichloroethane	10-42% of dose (3 days)			mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
$^{14}CO_2$	12-15% of dose (3 days)			mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
chloroacetic acid (a) figure represents the percentage of total radioactivity in urine, rather than percentage of dose. Total 14-C urinary activity was 51-73% of dose.		6-23%(a) (3 days)		mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1

1,2-DICHLOROETHANE (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
free S-carboxymethylcysteine		44-46%(a) (3 days)		mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
thiodiacetic acid		33-34%(a) (3 days)		mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
2-chloroethanol		0.0-0.8%(a) (3 days)		mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
Metabolite conjugates:					
S-carboxymethylcysteine		0.5-5%(a) (3 days)		mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
S,S'-ethylene-bis-cysteine		0.7-1.0%(a) (3 days)		mouse, 0.05, 0.10, 0.14 and 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1
S-(beta-hydroxyethyl-mercapturic acid		major metabolite		rat, 100 mg, stomach tube	N-2
S-(beta-hydroxyethyl) cysteine		trace amounts		rat, 100 mg, stomach tube	N-2
^{14}C-activity		51-73% (total for 3 days)		mouse, 0.05, 0.10, 0.14 or 0.17 g/kg ^{14}C-1,2-dichloroethane, i.p.	N-1



a) 1,1- dichloroethylene
b) chloroacetic acid
c) S-chlorocarbonylmethylcysteinyl-glutathione
d) S-carboxymethylcysteinylglutathione
e) N-acetyl-S-cysteinyl acetyl derivative
f) S-carboxymethylcysteine
g) thiodiglycollic acid
h) thioglycollic acid
j) dithioglycollic acid

Metabolic pathway for vinylidene chloride in mammals. From Ref. 0-3

	Breath	Urine	Blood	Comments	Ref.
Parent compound: unchanged 1,1-DCE	28%			rat, 50 mg (^{14}C)1,1-DCE per kg, oral	0-3
	20% (72 hrs)			rat, 50 mg (^{14}C)1,1-DCE per kg, oral	0-1
	0.9% (72 hrs)			rat, 0.5 mg (^{14}C)1,1-DCE per kg, oral	0-1
	6%			mouse, 50 mg (^{14}C)1,1-DCE per kg, oral	0-3
^{14}C-activity (a) total elimination; primarily urinary		97-99%(a) (72 hrs post-exposure)		rat, 10ppm (^{14}C) 1,1-DCE, inhalation, 6 hrs	0-2
		92%(a) (72 hrs post-exposure)		fasted rat, 200ppm (^{14}C) 1,1-DCE, inhalation, 6 hrs	0-2
		96%(a) (72 hrs post-exposure)		fed rat, 200ppm (^{14}C)1,1-DCE, inhalation, 6 hrs	0-2
		97-99%(a) (72 hrs)		rat, 1 mg (^{14}C)1,1-DCE per kg, oral dose	0-2
		60-75%(a) (72 hrs)		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-2
(b) primarily thiodiglycollic acid		52%(b) (72 hrs)		rat, 0.5 mg (^{14}C)1,1-DCE per kg, oral dose	0-1
		36%(b) (72 hrs)		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-1

1,1-DICHLOROETHYLENE
(VINYLIDENE CHLORIDE) (continued)

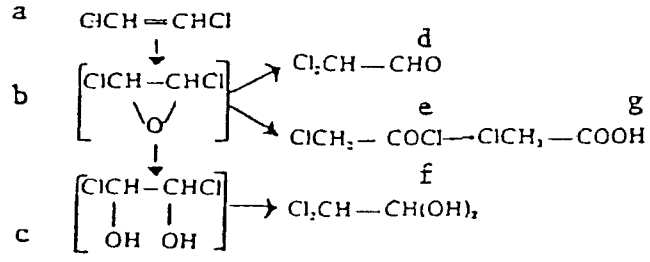
	Breath	Urine	Blood	Comments	Ref.
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
$^{14}CO_2$	23% (72 hrs)			rat, 0.5 mg (^{14}C)1,1-DCE per kg, oral dose	0-1
	6% (72 hrs)			rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-1
	3%			mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
	3.5%			rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
Metabolite conjugates:					
chloroacetic acid		1%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
dithioglycollic acid		23%		mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
		5%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
N-acetyl-S-(2-carboxy-methyl) cysteine		4%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
N-acetyl-S-cysteinyl acetyl derivative		50%		mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
		28%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
thiodigylcollic acid		3%		mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3

1,1-DICHLOROETHYLENE
(VINYLIDENE CHLORIDE) (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates (cont.)					
(thiodiglycollic acid, cont.)		22%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
thioglycollic acid		5%		mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
		3%		rat, 0.5 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
thioglycollyloxalic acid		3%		mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
		2%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
urea		3%		mouse, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3
		3.5%		rat, 50 mg (^{14}C)1,1-DCE per kg, oral dose	0-3

1,2-DICHLOROETHYLENE

Proposed metabolic pathway (by analogy to the metabolism of related compounds such as trichloroethylene)

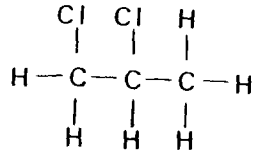


A proposed metabolic pathway of 1,2-dichloroethylene.

a) 1,2-dichloroethylene
b) 1,2-dichloroethylene epoxide
c) 1,2-dichloroglycol
d) dichloroacetaldehyde
e) monochloroacetyl chloride
f) 2,2-dichloro-1,1-ethanediol
g) monochloroacetic acid

No information was available on the distribution of 1,2-dichloroethylene in breath, urine, or blood. An in vitro study using rat liver homogenates reported small amounts of dichloroacetic acid and dichloroethanol after perfusion with cis or trans 1,2-DCE (P-1).

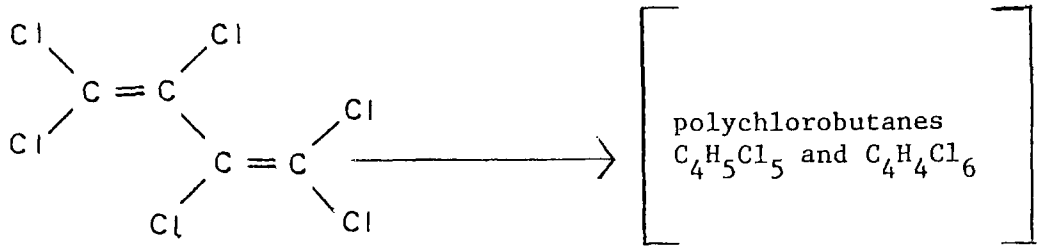
1,2-DICHLOROPROPANE



	Breath	Urine	Blood	Comments	Ref.
Parent compound:					
dichloropropane			0.6-1.1 mg/100 cc blood	rabbit, 1,500 ppm in air, 7 hrs/ day for 5 days	Q-1
			1.5-2.9 mg/100 cc blood	rabbit, 2,200 ppm in air, 7 hrs/ day for 5 days	Q-1
			1.3-1.6 mg/100 cc blood	dog, 1,000 ppm in air, 7 hrs/ day for 5 days	Q-1
volatile chlorinated hydrocarbons, probably unchanged 1,2-dichloro propane	23.1%			rat, 1.07 mg (10.3 uCi) of 1,2-dichloro-(1-^{14}C)propane, single oral dose	Q-2
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
$^{14}CO_2$	19.3%			rat, 1.07 mg (10.3 uCi) of 1,2-dichloro-(1-^{14}C)propane, single dose, by stomach tube	Q-2
radioactive substances		50.2%		rat, 0.88 mg (8.5 uCi) of 1,2-dichloro-(1-^{14}C)propane, in 0.5 ml arachis oil, single oral dose	Q-2
pigment-producing substance		present, but not identified or quantitated		rat, mouse, and guinea pig; dichloro-propane vapors, concentration not stated	Q-1
Metabolite conjugates:	No data	No data	No data		

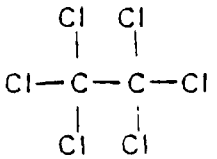
HEXACHLOROBUTADIENE

Based on findings of Murzakaev., (R-1)



hexachlorobutadiene

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
pentachlorobutane	No data	No data	No data		
Metabolite conjugates:	No data	No data	No data		



hexachloroethane

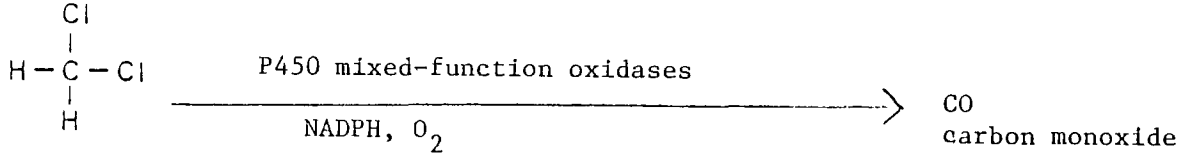
No data were available on the metabolic pathway of hexachloroethane.

	Breath	Urine	Blood	Comments	Ref.
Parent compound:					
hexachloroethane		50-70 ug/ml (24 hours)	10-28 ug/ml (24 hours)	sheep, 0.5 g/kg, single oral dose	S-2
			0.2 ug/g (6 hrs)	sheep (anaesthetized) 0.5 g/kg, single oral dose	S-2
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
trichloroethanol		1.3% (3 days)		rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1

HEXACHLOROETHANE (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
trichloroacetic acid		1.3% (3 days)		rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1
dichloroacetic acid		0.8% (3 days)		rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1
monochloroacetic acid		0.7% (3 days)		rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1
dichloroethanol		0.4% (3 days)		rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1
oxalic acid		0.1% (3 days)		rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1
volatile metabolites (includes CO_2, C_2Cl_6, tetrachloroethylene and 1,1,2,2-tetrachloroethane)	14-24%			rabbit, 0.5 g of ^{14}C-hexachloroethane/kg body wt., in diet	S-1
tetrachloroethylene		25-29 ug (24 hrs)	0.6-1.1 ug/ml (24 hrs)	sheep, 0.5 g/kg, single oral dose	S-2
			0.2-0.4 ug/ml (6 hrs)	sheep, 0.5 g/kg, single oral dose	S-2
pentachloroethane		20-25 ug (24 hrs)	0.06-0.5 ug/ml (24 hrs)	sheep, 0.5 g/kg, single oral dose	S-2
			0 - trace (6 hrs)	sheep, 0.5 g/kg, single oral dose	S-2
Metabolite conjugates:	No data	No data	No data		

Based on findings of Kubic and Anders. 1975. Metabolism of dihalomethanes to carbon monoxide II. Drug Metab. Dispos. 3(2): 104-112.



methylene chloride

	Breath	Urine	Blood	Comments	Ref.
Parent compound:					
^{14}C methylene chloride	77.0%, 92.0% (2 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
	95.3%, 92.6% (8 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
	91.50% (24 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
Half-life for elimination of COHb after methylene chloride exposure			13 hrs.	human, 8 hrs exposure to 180 ppm methylene chloride	T-4

Methylene chloride (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites:					
(C^{14})carbon dioxide	0.44%, 0.65% (2 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
	1.44%, 1.61% (8 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
	3.04% (24 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
carbon dioxide	29%			rat, 0.2 mmol/kg ^{14}C-methylene chloride inhalation (8 hrs), closed rebreathing system	T-2
(C^{14})carbon monoxide	0.14%, 0.14% (2 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals	T-1
	1.16%, 1.69% (8 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals	T-1
	2.15% (24 hrs)			rat, 412-930 mg/kg, i.p. Expressed as percentage of original dose. These are values for individual experimental animals	T-1

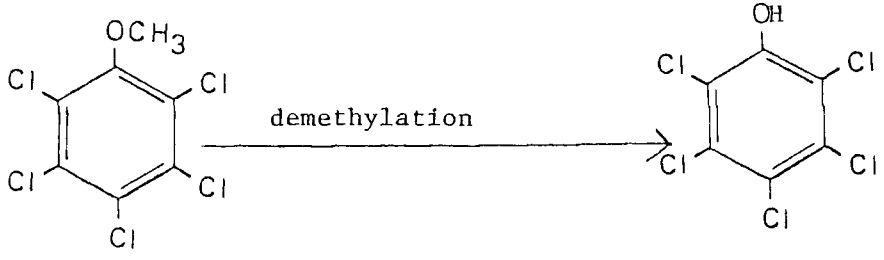
Methylene chloride (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont)					
carbon monoxide	47%			rat, 0.2 mmol/kg ^{14}C-methylene chloride inhalation (8 hrs), closed rebreathing system	T-2
			1.5% Hb saturation after 30 min. exposure	human, 213 ppm methylene chloride inhalation (60 min)	T-3
			1.75% Hb saturation after 60 min. exposure	human, 213 ppm methylene chloride inhalation (60 min)	T-3
			2.4% Hb saturation 3 hrs after exposure		
carbon monoxide as carboxyhemoglobin (COHb)			10.1% Hb saturation 1 hr post exposure	human, 986 ppm methylene chloride inhalation (2 hrs)	T-3
			9% Hb saturation	human, 180 ppm, workroom air (8 hrs)	T-4
			6% maximum Hb saturation	rat, 3.0 mmol/kg i.p. (after 2-2.5 hrs)	T-5
			7% maximum Hb saturation	rat, 440 ppm inhalation exposure (3 hrs)	T-6

Methylene chloride (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(^{14}C)-unidentified compound	0.34%, 0.46% (2 hrs)			rat, 412-930 mg/kg i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
	0.74%, 0.86% (8 hrs)			rat, 412-930 mg/kg i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
	1.49% (24 hrs)			rat, 412-930 mg/kg i.p. Expressed as percentage of original dose. These are values for individual experimental animals.	T-1
(^{14}C)-activity representing parent compound and metabolites	75% (2 hrs)			rat, 412-930 mg/kg methylene chloride, i.p. Expressed as percentage of orginial dose.	T-1
	98% (24 hrs)			rat, 412-930 mg/kg methylene chloride, i.p. Expressed as percentage of orginial dose.	T-1
		1.0% (24 hrs)		rat, 412-930 mg/kg methylene chloride, i.p. Expressed as percentage of orginial dose.	T-1
Metabolite conjugates:	No data	No data	No data		

PENTACHLOROANISOLE (PGA)



pentachloroanisole

pentachlorophenol

Based on findings of Glickman et al., (U-1)

	Breath	Urine	Blood	Comments	Ref.
Parent Compound:			approx. 1 ug/g (12 hrs)	rainbow trout, 0.024 mg ^{14}C PGA/L H_2O at 12°C for 12 hrs	U-1
Half-life of parent compound:			6.3 days	rainbow trout, 0.024 mg ^{14}C PGA/L H_2O at 12°C for 12 hrs	U-1
Metabolites:	No data	No data	No data		
Metabolite conjugates:	No data	No data	No data		

Metabolism of pentachlorobenzene, based on studies by Kohli et al., 1976 (Can. J. Biochem., 54(3): 203-208).

	Breath	Urine	Blood	Comments	Ref.
Parent Compound:	0			chinchilla doe, 0.5 mg/kg, by stomach tube	V-1
	0			chinchilla doe, 0.5 mg/kg, by subcutaneous injection	
		3% total excretion products (urine + feces)		rat, rate and route of administration unspecified	V-2
Half-life of parent compound:	No data	No data	No data		

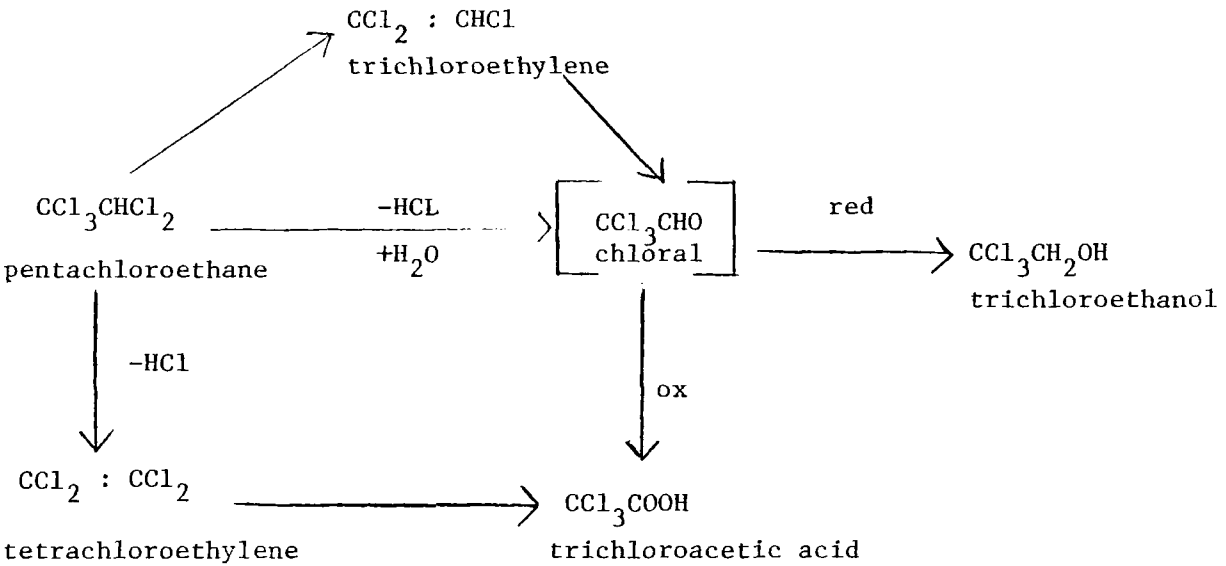
Pentachlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites:					
pentachlorophenol		9% total excretion products (urine + feces)		rat, rate and route of administration unspecified	V-2
tetrachlorophenol		unspecified amount		rat, rate and route of administration unspecified	V-2
tetrachlorohydroquinone		unspecified amount		rat, rate and route of administration unspecified	V-2
alpha-hydroxylated chlorothio compound		unspecified amount		rat, rate and route of administration unspecified	V-2
tri- or penta- chlorophenol		0.2% (3 days)		chinchilla doe, 0.5 mg/kg, by stomach tube	V-1
		0.2% (4 days)		chinchilla doe, 0.5 mg/kg, by stomach tube	V-1
		0.7% (7 days)		chinchilla doe, 0.5 mg/kg, by subcutaneous injection	V-1
other phenols		1% (3 and 4 days)		chinchilla doe, 0.5 mg/kg, by stomach tube	V-1
		1% (10 days)		chinchilla doe, 0.5 mg/kg, by subcutaneous injection	V-1
other chlorohydrocarbons	9% (3 days)			chinchilla doe, 0.5 mg/kg, by stomach tube	V-1
	21% (4 days)			chinchilla doe, 0.5 mg/kg, by stomach tube	V-1

Pentachlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(other chlorohydrocarbons, cont.)	2% (10 days)			chinchilla doe, 0.5 mg/kg, by subcutaneous injection	V-1
Metabolite conjugates:	No data	No data	No data		

PENTACHLOROETHANE



Metabolism of pentachloroethane, from Yllner, 1963 (W-1)

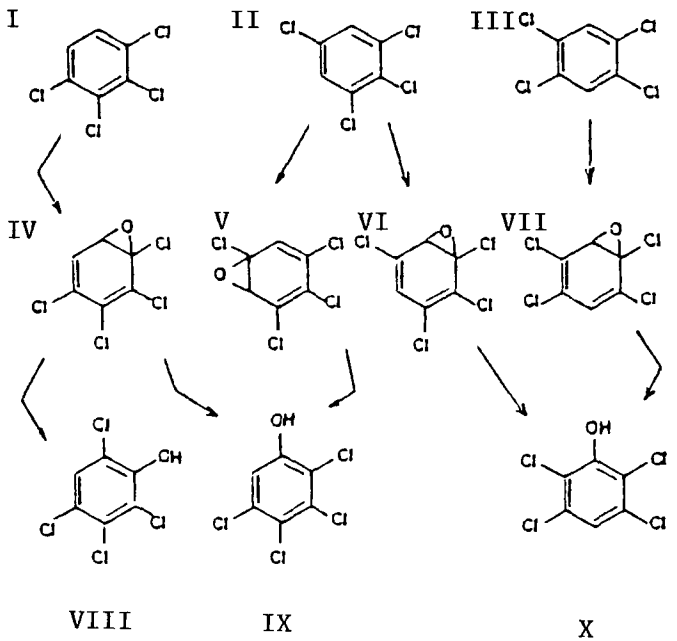
	Breath	Urine	Blood	Comments	Ref.
Parent compound:	present	present		unchanged pentachloroethane in the urine, feces and expired air accounted for approx. 30% (24 hrs) of the 20 ul dose injected subcutaneously in mice	W-1
			greater than 10^{-6} g/ml of of plasma (3 days), venous blood	sheep, 0.3 ml/kg single oral dose	W-2
	12-51% (3 days)			mouse, 1.1-1.8 g/kg injected subcutaneously	W-3

Pentachloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
tetrachloroethylene	present	present		tetrachloroethylene in the urine, feces and expired air accounted for 5% (24 hrs) of the 20 ul dose injected subcutaneously in mice	W-1
			greater than 10^{-6} g/ml of of plasma (3 days), venous blood	sheep, 0.3 ml/kg single oral dose	W-2
	3-9% (3 days)			mouse, 1.1-1.8 g/kg injected subcutaneously	W-3
trichloroethanol	present	present		tetrachloroethanol in the urine, feces and expired air accounted for 10% (24 hrs) of the 20 ul dose injected subcutaneously in mice	W-1
		16-32% (3 days)		mouse, 1.1-1.8 g/kg injected subcutaneously	W-3
trichloroacetic acid	present	present		trichloroacetic acid in the urine, feces and expired air accounted for 5% (24 hrs) of the 20 ul dose injected subcutaneously in mice	W-1
		9-18% (3 days)		mouse, 1.1-1.8 g/kg injected subcutaneously	W-3

Pentachloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
trichloroethylene	present	present		trichloroethylene in the urine, feces and expired air accounted for less than 5% (24 hrs) of the 20 ul dose injected subcutaneously in mice. The amount was not quantitated, but appeared to be less than the amount of tetrachloroethylene eliminated.	W-1
	2-16% (3 days)			mouse, 1.1-1.8 g/kg injected subcutaneously	W-3
Metabolite conjugates:	No data	No data	No data		



I) 1,2,3,4-tetrachlorobenzene
II) 1,2,3,5-tetrachlorobenzene
III) 1,2,3,5-tetrachlorobenzene
IV) 2,3,4,5-tetrachlorobenzene oxide
V) 1,3,4,5-tetrachlorobenzene oxide
VI) 2,3,4,6-tetrachlorobenzene oxide
VII) 2,3,5,6-tetrachlorobenzene oxide
VIII) 2,3,4,6-tetrachlorophenol
IX) 2,3,4,5-tetrachlorophenol
X) 2,3,5,6-tetrachlorophenol

Proposed metabolism of tetrachlorobenzene isomers, from Kohli et al., 1976 (X-1)

	Breath	Urine	Blood	Comments	Ref.
Parent Compound:					
1,2,3,4-isomer	8% (6 days)			chinchilla doe rabbits, 0.5 g/kg by stomach tube	X-2
1,2,4,5-isomer	2% (6 days)			chinchilla doe rabbits, 0.5 g/kg by stomach tube	X-2
1,2,3,5-isomer	12% (6 days)			chinchilla doe rabbits, 0.5 g/kg by stomach tube	X-2

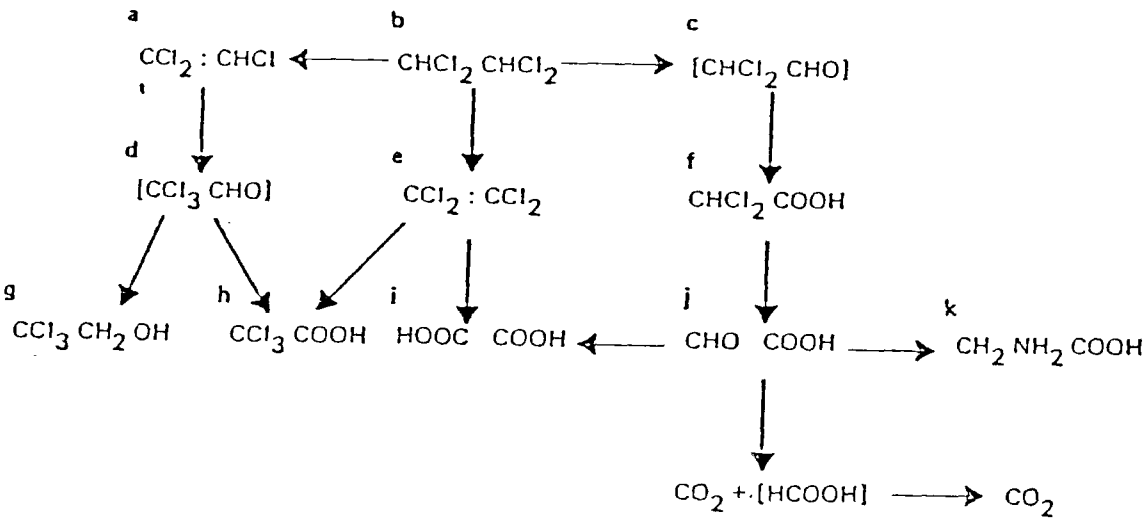
Tetrachlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Half-life of parent compound:	No data	No data	No data		
Metabolites of the 1,2,3,4-isomer:					
2,3,4,5-tetrachlorophenol		20% (10 days)		male rabbits, 300 mg/rabbit (4-5 kg), by i.p. injection	X-1
		43% (6 days)		chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2
other phenols		less than 1% (6 days)		chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2
mercapturic acid		less than 1% (6 days)		chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2
other chlorobenzenes		2% (2 days)		chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2
Metabolites of the 1,2,3,5-isomer:					
2,3,4,5-tetrachlorophenol		3% (10 days)		male rabbits, 300 mg/rabbit (4-5 kg), by i.p. injection	X-1
2,3,5,6-tetrachlorophenol		2% (10 days)		male rabbits, 300 mg/rabbit (4-5 kg), by i.p. injection	X-1
2,3,4,6-tetrachlorophenol		1.5% (10 days)		male rabbits, 300 mg/rabbit (4-5 kg), by i.p. injection	X-1
tetrachlorophenols (predominantly 2,3,4,6-tetrachlorophenol		5% (6 days)		chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2

Tetrachlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites of the					
1,2,3,5-isomer (cont.)					
other phenols		5% (6 days)		chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2
other chlorobenzenes	9% (6 days)			chinchilla doe rabbits, 0.5 g/kg, by stomach tube	X-2
Metabolites of the					
1,2,4,5-isomer:					
tetrachlorophenols		2% (6 days)		chinchilla doe rabbits, 0.5 g/kg by stomach tube	X-2
other phenols		5% (6 days)		chinchilla doe rabbits, 0.5 g/kg by stomach tube	X-2
other chlorobenzenes	10% (6 days)			chinchilla doe rabbits, 0.5 g/kg by stomach tube	X-2
Metabolite conjugates:	No data	No data	No data		

Adapted from the findings of Yllner, (Y-3)



a) trichloroethylene
b) tetrachloroethane
c) dichloroacetaldehyde
d) trichloroacetaldehyde
e) tetrachloroethylene
f) dichloroacetic acid
g) trichloroethanol
h) trichloroacetic acid
i) oxalic acid
j) glycine acid
k) glyceine

	Breath	Urine	Blood	Comments	Ref.
Parent compound:					
^{14}C-tetrachloroethane	4% (3 days)			mouse, 0.21-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
Metabolites:					
$^{14}CO_2$	50% (3 days)			mouse, 0.21-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3

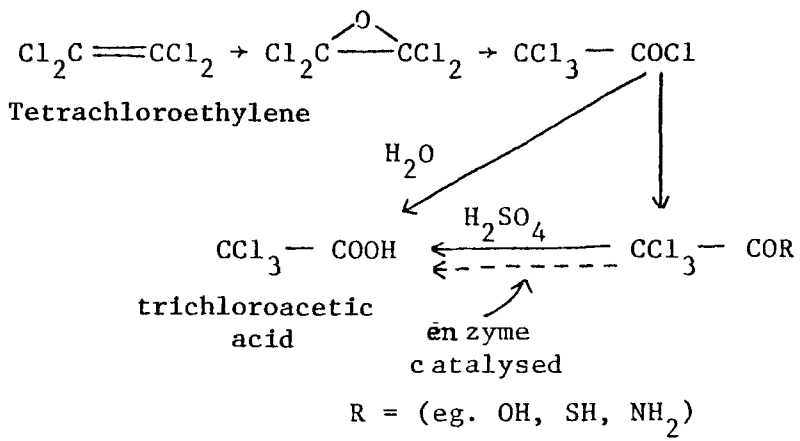
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
dichloroacetic acid		27% of urinary activity (24 hrs)		mouse, 0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
trichloroethanol		10% of urinary activity (24 hrs)		mouse, 0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
		8.2 mg/kg (48 hrs)		rat, 200 ppm, inhalation exposure (8 hrs)	Y-4
		0.8 mg/kg (48 hrs)		rat, 2.78 mmol/kg body wt, (equivalent to 467 mg/kg), i.p. injection	Y-4
		trace (96 hrs)		rat, 2.78 mmol/kg body wt, (equivalent to 467 mg/kg), i.p. injection	Y-4
oxalic acid		7% of urinary activity (24 hrs)		mouse, 0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
trichloroacetic acid		4% of urinary activity (24 hrs)		mouse, 0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
		1.7 mg/kg (48 hrs)		rat, 200 ppm, inhalation exposure (8 hrs)	Y-4
		1.3 mg/kg (48 hrs)		rat, 2.78 mmol/kg body wt, (equivalent to 467 mg/kg), i.p. injection	Y-4
		0.3 mg/kg (96 hrs)		rat, 2.78 mmol/kg body wt, (equivalent to 467 mg/kg), i.p. injection	Y-4

1,1,2,2-Tetrachloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
urea		2% of urinary activity (24 hrs)		mouse, 0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
glyoxylic acid		0.9% of urinary activity (24 hrs)		mouse, 0.16-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
chlorinated hydrocarbons		0.5 mg/L of urine		dog, (dose not stated) inhalation exposure (1 hr/day, up to 20 days)	Y-2
		0.5 mg/L of urine		rat, rabbit, and guinea pig (dose not stated), subcutaneous injection	Y-2
^{14}-C activity		28% (3 days)		mouse, 0.21-0.32 g ^{14}C-tetrachloroethane per kg body wt, i.p. injection	Y-3
^{38}Cl-activity	3.3% (1 hr) of retained radioactivity			human, 2.5 mg ^{38}Cl-tetrachloroethane inhaled; 97% of the dose was retained in the lungs	Y-3
Metabolite conjugates:	No data	No data	No data		

Proposed metabolism of Tetrachloroethylene. Bonse et al., (Z-2)

TETRACHLOROETHYLENE



	Breath	Urine	Blood	Comments	Ref.
Parent compound:	1 ppm 14 days after exposure			human, 100 ppm inhalation 7 hrs/day, 5 days	Z-7
	97.9% (48 hrs)			rat, 1.75 uCi, administered by stomach tube. Expressed as percentage of original dose.	Z-1
Half-life of parent compound:	3 days			human, 100 ppm inhalation 7 hr/day, 5 days	Z-7
	65 hrs	144 hrs		human, occupational exposure	Z-6
Half-life of metabolites:					
total trichloro compounds		123.3 hrs		human (male), 30-100 ppm, inhalation 8 hrs/day, 5 days/week, occupational exposure	Z-6

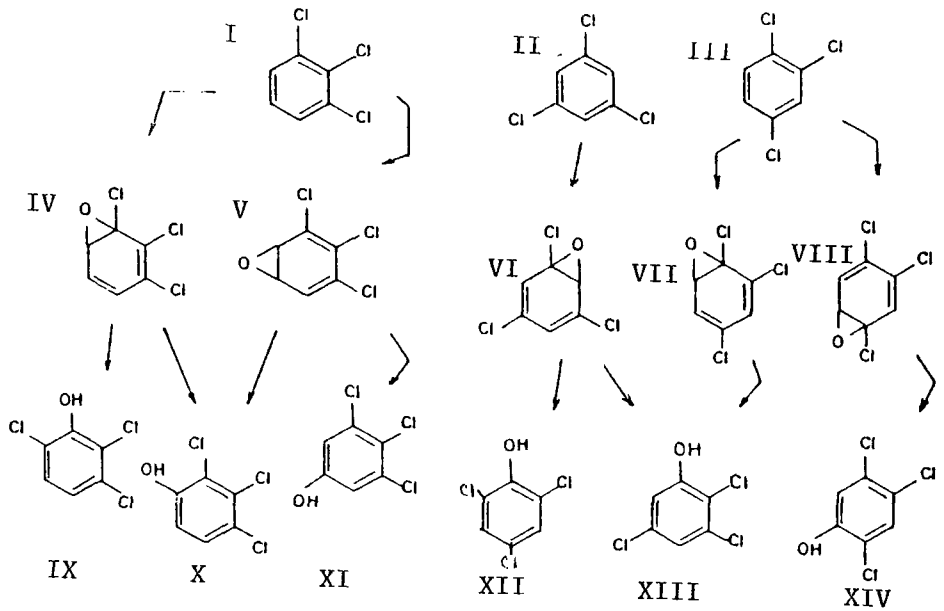
	Breath	Urine	Blood	Comments	Ref.
Half-life of metabolites (cont.)					
(total trichloro compounds, cont.)		190.1 hrs		human (female), 10-20 ppm, inhalation 8 hrs/day, 5 days/week, occupational exposure	Z-6
Metabolites:					
trichloroacetic acid		52%		mouse, 1.3 mg/g body wt, vapor,2 hrs, exposure. Figure represents percentage of urinary radioactivity. Urinary radioactivity was 20% of absorbed activity.	Z-3
		5.3 mg/kg body wt (48 hrs)		rat, 200 ppm inhalation exposure, 8 hrs	Z-4
		5.5 mg/kg body wt (48 hrs)		rat, 2.78 mmol/kg body wt, i.p.	Z-4
		4-35 mg/L		human, 20-70 ppm, daily, intermittent occupational exposure	Z-4
		32-97 mg/L		human, 200-400 ppm daily, intermitten occupational exposure	Z-4
		1.8% of retained tetrachloroethylene (67 hrs)		human, 87 ppm, inhalation exposure, 3 hrs	Z-5
trichloroethanol		3.2 mg/kg body wt. (48 hrs)		rat, 200 ppm, inhalation exposure, 8 hrs	Z-4

Tetrachloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)		0.08 mg/kg body wt (48 hrs)		rat, 2.78 mmol/kg body wt i.p.	Z-4
		4-20 mg/L		human, 20-70 ppm, daily, intermittent occupational exposure	Z-4
		21-100 mg/L		human, 200-400 ppm, daily, intermittent occupational exposure	Z-4
oxalic acid		11%		mouse, 1.3 mg/g body wt, vapor, 2 hrs exposure. Figure represents percentage of urinary radioactivity. Urinary activity was 20% of absorbed activity.	Z-3
dichloroacetic acid		trace amount		mouse, 1.3 mg/g body wt, vapor, 2 hrs exposure. Figure represents percentage of urinary radioactivity. Urinary activity was 20% of absorbed activity.	Z-3
unknown chloride		1.0% of retained tetrachloro-ethylene (67 hrs)		human, 87 ppm inhalation exposure, 3 hrs	Z-5
^{36}Cl-activity representing parent compound and/or metabolites	97.9% (48 hrs)	2.1% (48 hrs)		rat, 1.75 uCi, administered by stomach tube	Z-1

Tetrachloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
^{14}C activity representing parent compound and/or metabolites	70% of absorbed activity	20% of absorbed activity		mouse, 1.3 mg/g body wt inhalation, 2 hrs	Z-3
Metabolite conjugates:	*No data*	*No data*	*No data*		



I) 1,2,3-trichlorobenzene
II) 1,3,5-trichlorobenzene
III) 1,2,4-trichlorobenzene
IV) 2,3,4-trichlorobenzene oxide
V) 3,4,5-trichlorobenzene oxide
VI) 1,3,5-trichlorobenzene oxide
VII) 2,3,5-trichlorobenzene oxide
VIII) 2,4,5-trichlorobenzene oxide
IX) 2,3,6-trichlorophenol
X) 2,3,4-trichlorophenol
XI) 3,4,5-trichlorophenol
XII) 2,4,6-trichlorophenol
XIII) 2,3,5-trichlorophenol
XIV) 2,4,5-trichlorophenol

Metabolism of trichlorobenzene isomers based studies by Kohli et al., 1976 (AA-2).

	Breath	Urine	Blood	Comments	Ref.
1,2,3 isomer					
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
trichlorophenols (primarily 2,3,4-trichlorophenol; smaller amounts of 3,4,5-trichlorophenol and 3,4,5-trichlorocatechol)		78% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
2,3,4-trichlorophenol		11% (10 days)		rabbit, 300 mg, i.p.	AA-2

Trichlorobenzene (continued)

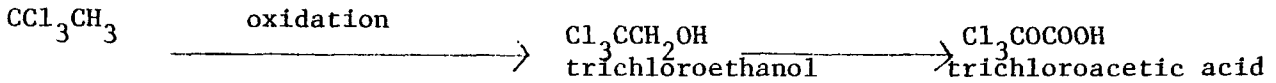
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
2,3,6-trichlorophenol		1% (10 days)		rabbit, 300 mg, i.p.	AA-2
3,4,5-trichlorophenyl acetate		2% (10 days)		rabbit, 300 mg, i.p.	AA-2
Metabolite conjugates:					
glucuronide		50% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
ethereal sulphate		12% (5 days)		rabbit, 0.5 g/kg by stomach tube	AA-1
2,3,4-trichlorophenyl-mercapturic acid		0.3% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1

Trichlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
1,2,4 isomer					
Parent compound:	No data	No data	No data		
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
trichlorophenols (2,4,5- and 2,3,5-trichlorophenol, plus small amounts of 3,4,6-trichlorocatechol)		42% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
2,4,5-trichlorophenol		5% (10 days)		rabbit, 300 mg, i.p.	AA-2
2,3,5-trichlorophenol		6% (10 days)		rabbit, 300 mg, i.p.	AA-2
Metabolite conjugates:					
glucuronide		27% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
ethereal sulphate		11% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
mercapturic acids (2,3,5- and 2,4,5-trichlorophenyl mercapturic acids)		0.3% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1

Trichlorobenzene (continued)

	Breath	Urine	Blood	Comments	Ref.
1,3,5 isomer:					
Parent compound:	12% (8 days)			rabbit, 0.5 g/kg, by stomach tube	AA-3
	8.5% (9 days)			rabbit, 0.5 g/kg, by stomach tube	AA-3
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
2,4,6-trichlorophenol		9%		rabbit, 0.5 g/kg, by stomach tube	AA-1
		3% (8 days)		rabbit, 0.5 g/kg, by stomach tube	AA-3
		10% (9 days)		rabbit, 0.5 g/kg, by stomach tube	AA-3
other phenols (4-chlorophenol and 4-chlorocatechol)		1% (8 days)		rabbit, 0.5 g/kg, by stomach tube	AA-3
		4% (9 days)		rabbit, 0.5 g/kg, by stomach tube	AA-3
monochlorobenzene	1% (8 or 9 days)			rabbit, 0.5 g/kg, by stomach tube	AA-3
Metabolite conjugates:					
glucuronide		20% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
ethereal sulphate		3% (5 days)		rabbit, 0.5 g/kg, by stomach tube	AA-1
mercapturic acid		0		rabbit, 0.5 g/kg, by stomach tube	AA-1



Proposed formation of urinary metabolites of 1,1,1-trichloroethane, from Ikeda and Ohtsuji, 1972 (AB-2)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:					
(a) alveolar air concentration of 1,1,1-trichloroethane	125 ppm (a) (at rest)			human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
	168 ppm (a) (50 W)			human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
	210 ppm (a) (100 W)			human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
	27 ppm (a) (150 W)			human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			3.0 ppm arterial blood (at rest)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			4.5 ppm arterial blood (50 W)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			5.2 ppm arterial blood (100 W)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			5.5 ppm arterial blood (150 W)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			1.4 ppm, venous blood (at rest)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			3.1 ppm, venous blood (50 W)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			3.5 ppm, venous blood (100 W)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
			4.4 ppm, venous blood (150 W)	human, 250 ppm exposure, 30 min. per exposure, at rest and with consecutive work loads of 50, 100, and 150 W as measured on a bicycle ergometer	AB-5
	179 ppm, alveolar air (at rest)			human, 350 ppm exposure, 30 min. per exposure, at rest and with 50 W work load as measured on a bicycle ergometer	AB-5
	239 ppm, alveolar air (50 W)			human, 350 ppm exposure, 30 min. per exposure, at rest and with 50 W work load as measured on a bicycle ergometer	AB-5

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			5.0 ppm, arterial blood (at rest)	human, 350 ppm exposure, 30 min. per exposure, at rest and with 50 W work load as measured on a bicycle ergometer	AB-5
			7.2 ppm, arterial blood (50 W)	human, 350 ppm exposure, 30 min. per exposure, at rest and with 50 W work load as measured on a bicycle ergometer	AB-5
			3.0 ppm, venous blood (at rest)	human, 350 ppm exposure, 30 min. per exposure, at rest and with 50 W work load as measured on a bicycle ergometer	AB-5
			4.0 ppm venous blood (50 W)	human, 350 ppm exposure, 30 min. per exposure, at rest and with 50 W work load as measured on a bicycle ergometer	AB-5
	128 ppm, alveolar air (at rest)			human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
	176 ppm, alveolar air (at rest plus 4% CO_2)			human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
	201 ppm, alveolar air (50 W plus 4% CO_2)			human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5

1,1,1-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			2.2 ppm, arterial blood (at rest)	human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
			3.3 ppm, arterial blood (at rest plus 4% CO_2)	human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
			3.9 ppm, arterial blood (50 W plus 4% CO_2)	human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
			1.0 ppm, venous blood (at rest)	human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
			1.2 ppm, venous blood (at rest plus 4% CO_2)	human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5
			1.9 ppm, venous blood (50 W plus 4% CO_2)	human, 250 ppm exposure, 30 min. per exposure; at rest, at rest plus 4% CO_2, and 50 W workload plus 4% CO_2	AB-5

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
	98.7% (25 hrs)			rat, 700 mg 1,1,1-trichloroethane-1-C^{14} per kg, i.p.	AB-1
	2.488 mg (1st hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	1.156 mg (2nd hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.589 mg (3rd hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.309 mg (4th hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.191 mg (5th hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.117 mg (6th hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.073 mg (7th hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.050 mg (8th hr)			rat, 221 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3

1,1,1-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
	5.719 mg (1st hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	3.350 mg (2nd hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	1.539 mg (3rd hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.793 mg (4th hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.441 mg (5th hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.259 mg (6th hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.154 mg (7th hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3
	0.098 mg (8th hr)			rat, 443 ppm, inhalation exposure (4 hrs); expired air level of parent compound measured hourly	AB-3

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			0.677-1.000 ug/mL	rat, 204 ppm inhalation exposure, 8 hrs/day, 5 days/week, 14 weeks; blood concentration of parent compound determined periodically for duration of exposure	AB-3
			0.08 nmol/g (17 hrs after last exposure)	rat, 20 umol/L (500 ppm), inhalation exposure, 6 hrs/day, 4 days	AB-8
			8.5 to 13.1 nmol/g (immediately after 2-6 hrs additional exposure on day 5)	rat, 20 umol/L (500 ppm), inhalation exposure, 6 hrs/day, 4 days	AB-8
			0.15 ug/g (3 hrs)	mouse, 10 ppm inhalation exposure for 3, 6, or 24 hours	AB-9
			0.47 ug/g (6 hrs)	mouse, 10 ppm inhalation exposure for 3, 6, or 24 hours	AB-9
			0.60 ug/g (24 hrs)	mouse, 10 ppm inhalation exposure for 3, 6, or 24 hours	AB-9
			3.0 ug/g (0.5 hr)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			4.8 ug/g (1 hr)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			4.2 ug/g (2 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			4.5 ug/g (3 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			8.1 ug/g (4 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			5.6 ug/g (4.5 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			6.2 ug/g (5 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			6.0 ug/g (6 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			5.8 ug/g (16 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			6.3 ug/g (24 hrs)	mouse, 100 ppm inhalation exposure for various exposure periods	AB-9
			31 ug/g (0.5 hr exposure)	mouse, 1000 ppm inhalation exposure for 0.5, 1, 3, 4.5, or 6 hours	AB-9
			38 ug/g (1 hr exposure)	mouse, 1000 ppm inhalation exposure for 0.5, 1, 3, 4.5, or 6 hours	AB-9
			41 ug/g (3 hrs exposure)	mouse, 1000 ppm inhalation exposure for 0.5, 1, 3, 4.5, or 6 hours	AB-9
			48 ug/g (4.5 hrs exposure)	mouse, 1000 ppm inhalation exposure for 0.5, 1, 3, 4.5, or 6 hours	AB-9
			36 ug/g (6 hrs exposure)	mouse, 1000 ppm inhalation exposure for 0.5, 1, 3, 4.5, or 6 hours	AB-9

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			103 ug/g (0.5 hr exposure)	mouse, 5,000 ppm inhalation exposure, for 0.5, 1, or 3 hours	AB-9
			144 ug/g (1 hr exposure)	mouse, 5,000 ppm inhalation exposure, for 0.5, 1, or 3 hours	AB-9
			165 ug/g (3 hrs exposure)	mouse, 5,000 ppm inhalation exposure, for 0.5, 1, or 3 hours	AB-9
			251 ug/g (0.5 hr exposure)	mouse, 10,000 inhalation exposure for 0.5, 3, or 6 hours	AB-9
			204 ug/g (3 hrs exposure)	mouse, 10,000 inhalation exposure for 0.5, 3, or 6 hours	AB-9
			404 ug/g (6 hrs exposure)	mouse, 10,000 inhalation exposure for 0.5, 3, or 6 hours	AB-9
Half-life of parent compound:		8.7 hrs (average)		human, occupational inhalation exposure to 4, 25, 28, or 53 ppm, for 8 hrs/day, 5-1/2 days/week, for at least 5 years (average)	AB-7
Metabolites:					
$^{14}CO_2$	0.5% (25 hrs)			rat, 700 mg 1,1,1-trichloroethane-1-C^{14} per kg, i.p.	AB-1
trichloroethanol		20.1 mg/24 hrs (1st day)		human, 500 ppm inhalation exposure 6 1/2-7 hrs/day, 5 days	AB-6
		30.1 mg/24 hrs (2nd day)		human, 500 ppm inhalation exposure 6 1/2-7 hrs/day, 5 days	AB-6

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)		29.3 mg/24 hrs (3rd day)		human, 500 ppm inhalation exposure 6 1/2-7 hrs/day, 5 days	AB-6
		46.6 mg/24 hrs (4th day)		human, 500 ppm inhalation exposure 6 1/2-7 hrs/day, 5 days	AB-6
		7.0 mg/24 hrs (6th day after last exposure)		human, 500 ppm inhalation exposure 6 1/2-7 hrs/day, 5 days	AB-6
		less than 1.0 mg/24 hrs (12th day after last exposure)		human, 500 ppm inhalation exposure 6 1/2-7 hrs/day, 5 days	AB-6
		1.2 mg/L (4.3 ppm exposure)		human, occupational inhalation exposure to 4.3, 24.6, or 53.4 ppm for 8 hrs/day, 5 1/2 days/week, for at least 5 years	AB-7
		5.5 mg/L (24.6 ppm exposure)		human, occupational inhalation exposure to 4.3, 24.6, or 53.4 ppm for 8 hrs/day, 5 1/2 days/week, for at least 5 years	AB-7
		9.9 mg/L (53.4 ppm exposure)		human, occupational inhalation exposure to 4.3, 24.6, or 53.4 ppm for 8 hrs/day, 5 1/2 days/week, for at least 5 years	AB-7

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)		3.1 mg/kg (48 hrs)		rat, 200 ppm inhalation exposure 8 hours	AB-2
		3.5 mg/kg (48 hrs)		rat, 2.78 mmol/kg, i.p.	AB-2
		126.2 ug (24 hrs)		rat, 221 ppm inhalation exposure 4 hours	AB-3
		7.5 ug (2nd 24-hr period)		rat, 221 ppm inhalation exposure, 4 hours	AB-3
		206.5 ug (24 hrs)		rat, 443 ppm inhalation exposure, 4 hrs	AB-3
		8.6 ug (2nd 24-hr period)		rat, 443 ppm inhalation exposure, 4 hrs	AB-3
			0.088 ug/ml (week 1)	rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks; trichloroethanol in blood measured periodically during exposure at 1,2,4 and 9 weeks	AB-3
			0.063 ug/ml (week 2)	rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks; trichloroethanol in blood measured periodically during exposure at 1,2,4 and 9 weeks	AB-3

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)			0.059 ug/ml (week 4)	rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks; trichloroethanol in blood measured periodically during exposure at 1,2,4 and 9 weeks	AB-3
			0.071 ug/ml (week 9)	rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks; trichloroethanol in blood measured periodically during exposure at 1,2,4 and 9 weeks	AB-3
		93.0 ug/24 hrs (week 1)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		222.9 ug/24 hrs (week 2)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		189.8 ug/24 hrs (week 3)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		216.3 ug/24 hrs (week 4)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)		254.5 ug/24 hrs (week 5)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		194.1 ug/24 hrs (week 6)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		302.8 ug/24 hrs (week 7)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		339.0 ug/24 hrs (week 8)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		383.9 ug/24 hrs (week 9)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		435.1 ug/24 hrs (week 10)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3

1,1,1-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites, (cont.)					
(trichloroethanol, cont.)		305.7 ug/24 hrs (week 11)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		291.7 ug/24 hrs (week 12)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		372.2 ug/24 hrs (week 13)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
		362.2 ug/24 hrs (week 14)		rat, chronic inhalation exposure, 204 ppm for 8 hrs/day, 5 days/week for 14 weeks, trichloroethanol in urine measured weekly	AB-3
trichloroacetic acid		7.5 mg/24 hrs (1st day)		human, 500 ppm, inhalation exposure, 6 1/2-7 hrs/day, 5 days	AB-6
		10.9 mg/24 hrs (2nd day)		human, 500 ppm, inhalation exposure, 6 1/2-7 hrs/day, 5 days	AB-6
		12.3 mg/24 hrs (3rd day)		human, 500 ppm, inhalation exposure, 6 1/2-7 hrs/day, 5 days	AB-6
		14.1 mg/24 hrs (4th day)		human, 500 ppm, inhalation exposure, 6 1/2-7 hrs/day, 5 days	AB-6

1,1,1-Trichloroethane (continued)

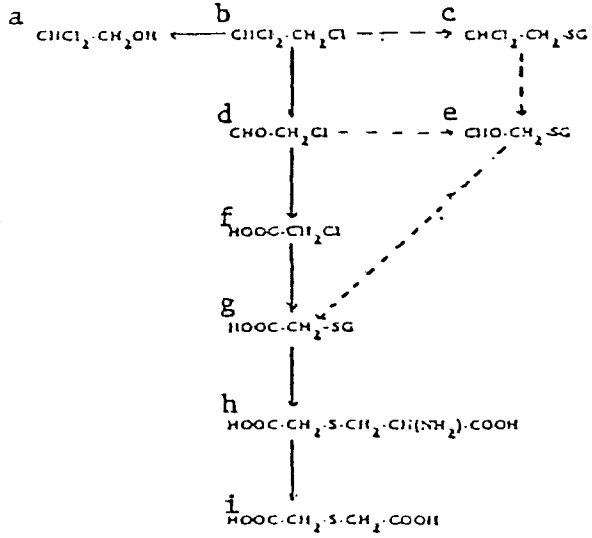
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroacetic acid, cont.)		18.0 mg/24 hrs (6th day after last exposure)		human, 500 ppm, inhalation exposure, 6 1/2-7 hrs/day, 5 days	AB-6
		17.5 mg/24 hrs (12th day after last exposure		human, 500 ppm, inhalation exposure, 6 1/2-7 hrs/day, 5 days	AB-6
		0.6 mg/L (4.3 ppm exposure)		human, occupational inhalation exposure to 4.3, 24.6, or 53.4 ppm for 8 hrs/day, 5 1/2 days/week, for at least 5 years	AB-7
		2.4 mg/L (24.6 ppm exposure)		human, occupational inhalation exposure to 4.3, 24.6, or 53.4 ppm for 8 hrs/day, 5 1/2 days/week, for at least 5 years	AB-7
		3.6 mg/L (53.4 ppm exposure)		human, occupational inhalation exposure to 4.3, 24.6, or 53.4 ppm for 8 hrs/day, 5 1/2 days/week, for at least 5 years	AB-7
		0.5 mg/kg body wt (48 hrs)		rat, 200 ppm inhalation exposure, 8 hours	AB-2
		0.5 mg/kg body wt (48 hrs)		rat, 2.78 mmol/kg, i.p.	AB-2

1,1,1-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroacetic acid, cont.)		0.3 mg/kg body wt (2nd 48-) hr period)		rat, 2.78 mmol/kg, i.p.	AB-2
		3.2 ug (24 hrs)		rat, 221 ppm inhalation exposure, 4 hrs	AB-3
		8.1 ug (2nd 24-) hr period)		rat, 221 ppm inhalation exposure, 4 hrs	AB-3
		9.5 ug (24 hrs)		rat, 443 ppm inhalation exposure, 4 hours	AB-3
		10.6 ug (2nd 24- hr period)		rat, 443 ppm inhalation exposure, 4 hours	AB-3
		7.5 ug (3rd 24- hr period)		rat, 443 ppm inhalation exposure, 4 hours	AB-3
		12-20 ug (daily average)		rat, 204 ppm inhalation exposure, 8 hrs/day, 5 days/week, for 14 weeks	AB-3

1,1,1-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolite conjugates:					
^{14}C-activity, primarily 2,2,2-trichloroethanol-2-C^{14} glucuronide		0.85% (24 hrs)		rat, 700 mg 1,1,1-trichloroethane-1-C^{14} per kg, i.p.	AB-1
Other:					
^{38}Cl-activity	44%			human, 5 mg ^{38}Cl-1,1,1-trichloroethane, inhalation (single breath)	AB-4
^{14}C-activity			0.02% (25 hrs)	rat, 700 mg 1,1,1-trichloroethane-1-C^{14} per kg, i.p.	AB-1



a) 2,2-dichloroethanol
b) 1,1,2-trichloroethane
c) S-(2,2-dichloroethyl)-glutathione
d) chloroacetaldehyde
e) S-formylmethylglutathione
f) chloroacetic acid
g) S-carboxymethylglutathione
h) S-carboxymethylcysteine
i) thiodiacetic acid

The full arrows indicate the suggested routes and the dotted arrows the alternatives.

Metabolic fate of 1,1,2-trichloroethane. (From ref. AC-1)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	approx. 6.4-8.8% (3 days)			mouse, 0.1-0.2 g ^{14}C-1,1,2-trichloroethane per kg, i.p.	AC-1
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
$^{14}CO_2$	approx. 9.6-13.2% (3 days)			mouse, 0.1-0.2 g ^{14}C-1,1,2-trichloroethane per kg, i.p.	AC-1

1,1,2-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
trichloroethanol		0.3 mg/kg body wt (48 hrs from start of exposure)		rat, 200 ppm inhalation exposure, 8 hours	AC-2
		0.2 mg/kg body wt (48 hrs from start of exposure)		rat, 2.78 mmol/kg, i.p.	AC-2
		trace (2nd 48-hr period		rat, 2.78 mmol/kg, i.p.	AC-2
2,2,2-trichloroethanol		0.2% of total urinary radiocativity; equivalent to about 0.16% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1
2,2,-dichloroethanol		1.4% of total urinary radiocativity; equivalent to about 1.12% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1

1,1,2-Trichloroethane (continued)

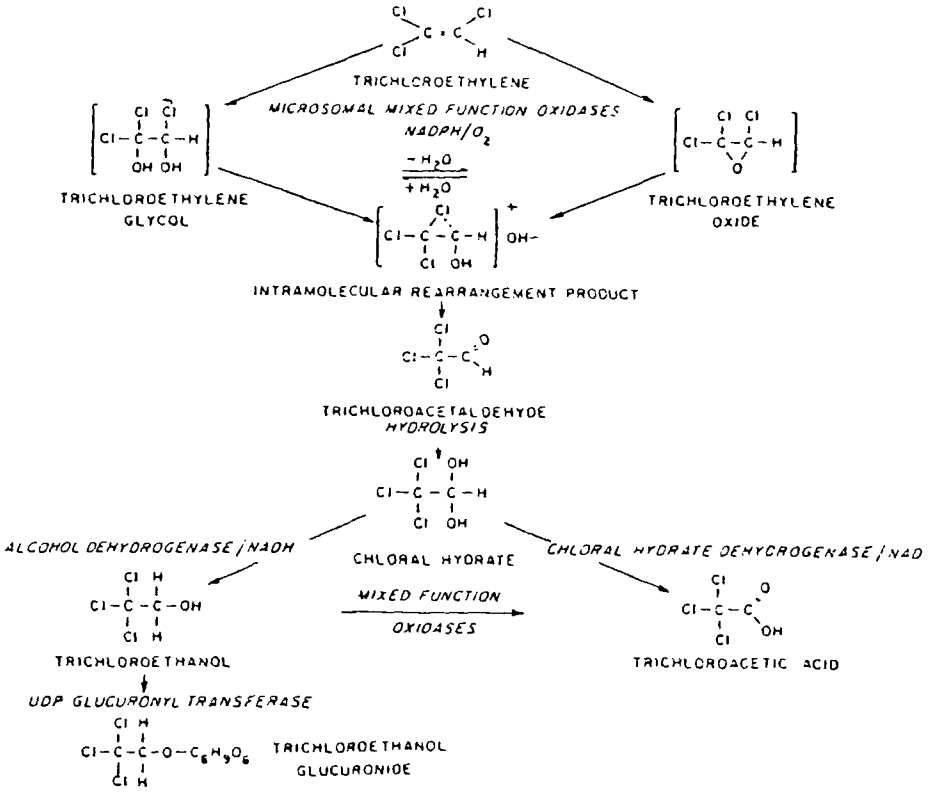
	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
trichloroacetic acid		0.3 mg/kg body wt (48 hrs from start of exposure)		rat, 200 ppm inhalation exposure, 8 hours	AC-2
		0.4 mg/kg body wt (48 hrs)		rat, 2.78 mmol/kg, i.p.	AC-2
		0.3 mg/kg body wt (2nd 48-hr period)		rat, 2.78 mmol/kg, i.p.	AC-2
		1.9% of total urinary radioactivity; equivalent to about 1.52% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1
chloroacetic acid		16.% of total urinary radioactivity; equivalent to about 12.78% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
S-carboxymethylcysteine		38.% of total urinary radioactivity; equivalent to about 30.36% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1
conjugated S-carboxymethylcysteine		5.% of total urinary radioactivity; equivalent to about 4.0% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1
thiodiacetic acid		40% of total urinary radioactivity; equivalent to about 31.96% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1
oxalic acid		0.4% of total urinary radioactivity; equivalent to about 0.32% of ^{14}C-1,1,2-trichloroethane dose (3 days)		mouse, 0.1-0.2 g of ^{14}C-1,1,2-trichloroethane, i.p.	AC-1

1,1,2-Trichloroethane (continued)

	Breath	Urine	Blood	Comments	Ref.
Other:					
^{38}Cl radioactivity	2.9% (1 hr)			human, about 5 mg of ^{38}Cl-1,1,2-trichloroethane, inhaled in a single breath	AC-3

TRICHLOROETHYLENE
(TCE)



Proposed intermediary metabolism of TCE. (AD-1)

	Breath	Urine	Blood	Comments	Ref.
Parent compound:	27.7% of retained TCE			human, male, inhalation exposure, concentration of TCE not stated	AD-8
	18.6% of retained TCE			human, female, inhalation exposure, concentration of TCE not stated	AD-8
	25.% of inhaled TCE concentration			human, 0.537 or 1.074 ppm inhalation, for 30 min., at rest	AD-7
	19.% of retained TCE			human, male, 27 ppm inhalation exposure, 4 hours	AD-5
	16.% of retained TCE			human, male, 81 ppm inhalation exposure, 4 hours	AD-5

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
	13.% of retained TCE			human, male, 201 ppm inhalation exposure, 4 hours	AD-5
	19.2% of retained TCE			human, male, 320 ppm inhalation exposure, 160 min	AD-4
	12.7% of retained TCE			human, female, 320 ppm inhalation exposure, 160 min	AD-4
	10% of retained TCE			human, male, 70 or 140 ppm inhalation exposure, with or without 100 W workload, for 4 hours	AD-6
	8% of retained TCE			human, male, 54 or 97 ppm inhalation exposure, 8 hours	AD-3
	72.1%			rat, 4.0 uCi of ^{38}Cl-trichloroethylene, by stomach tube	AD-2
	82.3%			rat, 7.5 uCi of ^{38}Cl-trichloroethylene, by stomach tube	AD-2
	84.8%			rat, 8.6 uCi of ^{38}Cl-trichloroethylene, by stomach tube	AD-2
			41.3 mg% (in blood cellular components)	rat, 10 mg/L, inhalation (exposure period not stated)	AD-1

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Parent compound (cont.)					
			2.5 mg% in blood plasma	rat, 10 mg/L, inhalation (exposure period not stated)	AD-1
		trace amount		calf, 3 or 12 g, oral dose, daily for 4 or 5 days	AD-14 and AD-15
Half-life of parent compound:	No data	No data	No data		
Metabolites:					
trichloroethanol		50% total amount excreted (350 hrs, avg.)		humans, male and female, 500-850 ug/L inhalation exposure for 5 hours	AD-9
		45.4% (3 weeks)		humans, male and female, 1042 ug/L inhalation exposure for 8 hours	AD-10
		32.7% (several weeks)		human, male, 54 or 97 ppm inhalation exposure for 8 hours	AD-3
		48.6% of of retained TCE (6 days)		human, male, 250-380 ppm inhalation exposure, 160 minutes	AD-4
		42.7% of of retained TCE (6 days)		human, female, 250-380 ppm inhalation exposure, 160 minutes	AD-4
		53.1% (100 hrs)		human, male, 170 ppm inhalation exposure for 3 hours	AD-11

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)		44% (100 hrs)		human, male, 170 ppm inhalation exposure for 7 hours (with a 1-hour break)	AD-11
		46.1% (16 or 21 days)		human, female, 1 mg/L inhalation exposure for 5 hours	AD-12
		25.1 mg/L (3 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		24.9 mg/L (5 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		42.0 mg/L (10 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		77.3 mg/L (25 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		220.3 mg/L (40 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)					
		256.7 mg/L (45 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		267.3 mg/L (50 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		307.7 mg/L (60 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		681.8 mg/L (120 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		973.1 mg/L (175 ppm exposure)		human, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
			1.7 ug/ml (1st exposure day)	human, male, 50 ppm inhalation exposure, 6 hrs/day for 5 days. Trichloroethanol level was measured daily, nonglucuronized fraction only. Figures represent maximum levels attained.	AD-16
			2.1 ug/ml (2nd exposure day)	human, male, 50 ppm inhalation exposure, 6 hrs/day for 5 days. Trichloroethanol level was measured daily, nonglucuronized fraction only. Figures represent	AD-16

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)			2.2 ug/ml (3rd exposure day)	human, male, 50 ppm inhalation exposure, 6 hrs/day for 5 days. Trichloroethanol level was measured daily, nonglucuronized fraction only. Figures represent maximum levels attained.	AD-16
			2.3 ug/ml (4th exposure day)	human, male, 50 ppm inhalation exposure, 6 hrs/day for 5 days. Trichloroethanol level was measured daily, nonglucuronized fraction only. Figures represent maximum levels attained.	AD-16
			2.3 ug/ml (5th exposure day)	human, male, 50 ppm inhalation exposure, 6 hrs/day for 5 days. Trichloroethanol level was measured daily, nonglucuronized fraction only. Figures represent maximum levels attained.	AD-16
			1.28-2.85 ug/ml (1st exposure day)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of Trichloroethanol were determined daily during and after exposure.	AD-17
			1.44-2.91 ug/ml (2nd exposure day)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)			2.01-2.53 ug/ml (3rd exposure day)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			1.57-2.58 ug/ml (4th exposure day)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			1.97-2.87 ug/ml (5th exposure day)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.51-2.11 ug/ml (1st day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.18-0.51 ug/ml (2nd day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)			0.03-0.27 ug/ml (3rd day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.05-0.14 ug/ml (4th day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.03-0.08 ug/ml (5th day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.05 ug/ml (6th day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.03 ug/ml (7th day post-exposure)	humans, male and female, 48 ppm inhalation exposure, 4 hrs/day for 5 days. Blood levels of trichloroethanol were determined daily during and after exposure.	AD-17
			0.71-1.78 ug/ml (immediately after exposure)	human, female, 40 or 44 ppm inhalation exposure. Refer to reference AD-17 for additional details and data.	AD-17

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)			0.47-0.70 ug/ml (24 hrs from start of exposure)	human, female, 40 or 44 ppm inhalation exposure. Refer to reference AD-17 for additional details and data.	AD-17
			less than 0.12 ug/ml (96 hrs from start of exposure)	human, female, 40 or 44 ppm inhalation exposure. Refer to reference AD-17 for additional details and data.	AD-17
			0.78-1.32 ug/ml (immediately after expsoure)	human, male, 40 or 44 ppm inhalation exposure. Refer to reference AD-17 for additional details and data.	AD-17
			0.24-0.55 ug/ml (24 hrs from start of exposure)	human, male, 40 or 44 ppm inhalation exposure. Refer to reference AD-17 for additional details and data.	AD-17
			trace (96 hrs from start of exposure)	human, male, 40 or 44 ppm inhalation exposure. Refer to reference AD-17 for additional details and data.	AD-17
			2.0 ug/ml (maximum level attained during exposure)	human, male, 50 ppm inhalation exposure, 6 hours/day, 5 days	AD-18
			2.5 ug/ml (maximum level attained during exposure)	human, male, inhalation exposure, 12 mins/hrs, 6 hrs/day 5 days	AD-18

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroethanol, cont.)			5.0 ug/ml (maximum level attained during exposure)	human, male, 100 ppm inhalation exposure, 6 hrs/day, 5 days	AD-18
		15-20% (4 days)		dog, dose and method not stated	AD-14
		15%		rat, oral administration, dose not stated	AD-14
		10-15%		rat, ^{38}Cl-TCE, dose not stated; administered by stomach tube	AD-14
		13-25%		calf, 3 or 12 g, oral, daily for 4 or 5 days	AD-14 and AD-15
trichloracetic acid		19%, total amount excreted (387 hrs, avg.)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
		31.9% (3 weeks)		humans, male and female, 1042 ug/L inhalation exposure for 8 hours	AD-10
		17.7% (several weeks)		humans, male, 54 or 97 ppm inhalation exposure for 8 hours	AD-3
		32.6% (6 days)		humans, male, 250-380 ppm inhalation exposure, 160 minutes	AD-4
		43.9% (6 days)		humans, female, 250-380 ppm inhalation exposure, 160 minutes	AD-4

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroacetic acid, cont.)		21.9% (100 hrs)		humans, male, 170 ppm inhalation exposure for 3 hours	AD-11
		18.1% (100 hrs)		humans, male, 170 ppm inhalation exposure for 7 hours (with a 1-hour break)	AD-11
		30.1% (16 or 21 days)		humans, female, 1 mg/L inhalation exposure for 5 hours	AD-12
		12.7 mg/L (3 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		20.2 mg/L (5 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		17.6 mg/L (10 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		77.2 mg/L (25 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroacetic acid, cont.)		90.6 mg/L (40 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		138.4 mg/L (45 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		146.4 mg/L (50 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		155.4 mg/L (60 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		230.1 mg/L (120 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		235.8 mg/L (175 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroacetic acid, cont.)			17 ug/ml (1st exposure day)	humans, male, 50 ppm inhalation exposure, 6 hours/day for 5 days. Figures represent maximum levels attained daily in plasma.	AD-16
			30 ug/ml (2nd exposure day)	humans, male, 50 ppm inhalation exposure, 6 hours/day for 5 days. Figures represent maximum levels attained daily in plasma.	AD-16
			38 ug/ml (3rd exposure day)	humans, male, 50 ppm inhalation exposure, 6 hours/day for 5 days. Figures represent maximum levels attained daily in plasma.	AD-16
			45 ug/ml (4th exposure day)	humans, male, 50 ppm inhalation exposure, 6 hours/day for 5 days. Figures represent maximum levels attained daily in plasma.	AD-16
			52 ug/ml (5th exposure day)	humans, male, 50 ppm inhalation exposure, 6 hours/day for 5 days. Figures represent maximum levels attained daily in plasma.	AD-16
			2.4 mg/100 ml of plasma (3rd day post-exposure)	humans, male and female, 1042 ug/L inhalation exposure for 5 hours	AD-20
			0.5 mg/100 ml of red cell mass (3rd day post-exposure)	humans, male and female, 1042 ug/L inhalation exposure for 5 hours	AD-20

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(trichloroacetic acid, cont.)		5-8% (4 days)		dog, dose and method not stated	AD-14
		4%		rat, inhalation exposure, dose not stated	AD-14
		1%		calf, 3 or 12 g, oral dose, daily for 4 or 5 days	AD-14 and AD-15
monochloroacetic acid		4%, total amount excreted (112 hrs. avg.)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
total trichloro-compounds					
		39.4 mg/L (3 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		45.6 mg/L (5 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		60.5 mg/L (10 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Metabolites (cont.)					
(total trichloro-compounds, cont.)					
		164.3 mg/L (25 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		324.9 mg/L (40 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		399.0 mg/L (45 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		418.9 mg/L (50 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		468.0 mg/L (60 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13
		915.3 mg/L (120 ppm exposure)		humans, male, occupational exposure (8 hrs/day, 6 days/week) to various concentrations of TCE, specified in parentheses	AD-13

Trichloroethylene (continued)

	Breath	Urine	Blood	Comments	Ref.
Half-life of metabolites:					
trichloroethanol		24 hours in 1st phase of excretion (first 3-4 days)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
		40 hours in 2nd phase of excretion (second 7-9 days)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
trichloroacetic acid		50 hours in 1st phase of excretion (first 5 days)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
		70 hours in 2nd phase of excretion (second 14 days)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
monochloroacetic acid		15 hours (total period of excretion was 112 hours, avg.)		humans, male and female, 500-850 ug/L inhalation exposure for 8 hours	AD-9
Metabolite conjugates:	No data	No data	No data		

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16. ABSTRACT

In response to growing concern about halogenated hydrocarbons (HHC's) identified as environmental pollutants and potential health hazards, the Office of Program Integration and Information's Monitoring Division is currently conducting a preliminary assessment of HHC's in man and environmental media. This report, which represents an initial effort in the program, is a summary of the available information on the metabolism of 49 selected HHC's. It includes 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. The report includes, as an appendix, a tabulary summary of the experimental data reported.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Metabolism Metabolites Metabolic pathways Halogenated hydrocarbons Halocarbons		

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