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

First Update

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FIRST UPDATE

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TABLE OF CONTENTS

	Page
INTRODUCTION	iv
METABOLISM REPORTS:	
Bromobenzene	1
Bromoform	2
Carbon Tetrachloride	3
o-Chlorobenzaldehyde	4
Chloroform	5
Chloronaphthalene	6
p-Dichlorobenzene	7
1,2-Dichloroethane	8
1,1-Dichloroethylene	10
Hexachlorobenzene	14
Lindane	18
Methylene Chloride	21
Pentachloroanisole	24
Pentachlorobenzene	25
Pentachlorophenol	27
Tetrachloroethylene	29
Tetrachlorophenol	32
1,2,4-Trichlorobenzene	34
Trichloroethylene	35

Introduction

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

The major thrust of the 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). To complement the RTI effort, Tracor-Jitco, Inc., under contract to the EPA, conducted a literature survey on the metabolism of selected halocarbons for use in evaluating the human body burden associated with environmental exposure. The result of this project was the publication of Metabolism Summaries of Selected Halogenated Organic Compounds in Human and Environmental Media, A Literature Survey EPA 560/6-79-008, April 1979.

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

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

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

3. halocarbon mutagenicity and carcinogenicity data.

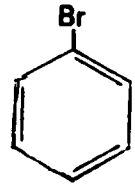
Details of HHC selection process are included in the report produced by RTI entitled Formation of A Preliminary Assessment of Halogenated Organic Compounds in Man and Environmental Media EPA 560/13-79-006.

The first literature survey provided metabolism summaries as well as basic information on the physical properties of the 30 HHC's reviewed. This present report updates information on 15 of the original HHC's plus provides physical data and metabolism summaries for four additional HHC's not included in the first survey.

Basic information on the physical properties of the compounds at the beginning of each summary include molecular and structural formulas, the Chemical Abstracts Registry (CAS) number, accepted synonyms, molecular weight (mol wt), boiling point (bp), and vapor pressure (vp). The text summarizes the available information on the uptake and retention of the compound, its subsequent distribution and elimination patterns, the identification and observed concentrations of metabolites, and the metabolic pathways involved.

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)

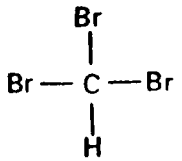
Urinary metabolites of bromobenzene in rats were reported by Mizutani et al. (1). The levels of bromo(methylthio)benzenes and their precursors did not increase when rats were given a higher amount of bromobenzene or were pretreated with diethyl maleate. Isomeric bromo(methylthio)benzenes were identified by gas chromatographic and mass spectral comparisons with authentic samples. The three peaks were identified as p-, m-, and o-bromo(methylthio)benzenes. In addition, they also recorded two known metabolites trans-1,2-dihydro-1,2-dihydroxy-3-bromobenzene and trans-1,2-dihydro-1,2-dihydroxy-4-bromobenzene. The authors suggested that isomeric metabolites of bromobenzene were not formed due to the covalent binding of bromobenzene to liver tissue.

Reference

1. Mizutani, T., K. Yamamoto, and K. Tajima. 1978. Bromo-(methylthio)benzenes and related sulfur-containing compounds minor urinary metabolites of bromobenzene in rats. Biochem. & Biophys. Res. Commun. 82(3):805-810.

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)

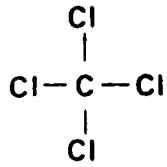
Anders et al. (1) reported in vivo studies in rats concerning metabolism of haloforms to carbon monoxide. The administration of ^{13}C labeled bromoform ($CHBr_3$) led to the formation of similarly enriched ^{13}CO. A dose-dependent relationship between $CHBr_3$ dose and CO production was observed. Phenobarbital (but not 3-methyl-cholanthrene) treatment increased the blood CO levels soon after the administration of $CHBr_3$, but no increase occurred in the saline-treated controls. In addition, lower blood CO levels were found in rats give ^{2}H-bromoform as compared to rats given bromoform. Administration of either diethylmaleate or D-penicillamine did not alter the blood CO level produced in response to bromoform administration. The in vivo metabolism of haloforms to CO followed the halide order; thus, administration of iodoform yielded the highest blood CO levels, whereas chloroform yielded the lowest levels.

Reference

1. Anders, M.W., O.L. Stevens, R.W. Spraque, Z. Shaath and A.E. Ahmed. 1978. Metabolism of haloforms to carbon monoxide. II. In vivo studies. Metabolism and Disposition 6(5):556-560.

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)

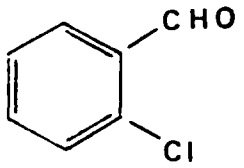
Kubic and Anders (1) reported the metabolism of carbon tetrachloride (CCl_4) to phosgene in rats hepatic microsomal fractions. Rats were pretreated with 50 mg/kg phenobarbital for 4 days before sacrifice. Hepatic microsomal fractions were prepared and incubated for 15 min in reactions mixtures of 32.5 μmoles CCl_4 and 4 μmoles of NADPH in buffered medium. Samples were then quantitatively analyzed by gas chromatography-mass spectrometry. Phosgene was identified as a metabolite of CCl_4 in this experiment. Phosgene was identified as the adduct, 2-oxothiazolide-4-carboxylic acid, formed with its reaction with cysteine. $[^{13}C]$-CCl_4 was metabolized to 2-$[^{13}C]$-oxothiazolidene-4-carboxylic acid and when CCl_4 was incubated in the presence of $[^{18}O]$-O_2, 2-$[^{18}O]$-oxothiazolidine-4-carboxylic acid was produced. The metabolism of CCl_4 to phosgene may be an important factor in the hepatotoxicity of CCl_4.

Reference

1. Kubic, V.L. and M.W. Anders. 1980. Metabolism of carbon tetrachloride to phosgene. Life Sci. 26: 2151-2155.

o-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)

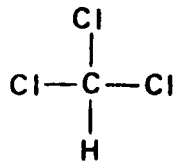
Caszynski et al. (1) investigated the suitability of experimental bypass of the rabbit liver and kidney to study the biotransformation of rapidly metabolized substances using o-chlorobenzylidenemalonic nitrile as a model compound. The animals were exposed to this compound by intravenous administration of 9.1 mg/kg. The two major metabolites identified were o-chlorobenzaldehyde and o-chlorobenzylmalonic nitrile. In the animals with liver bypass, approximately 90% of the parent compound was metabolized, whereas only 30% was metabolized in the control animals.

Reference

1. Caszynski, W., M. Paradowski and S. Andrzejewski. 1978. Experimental bypass of the liver and kidneys in rabbits as a method for studying the biotransformation of rapidly metabolized substances. Anest. Reanim. Intensywna Ter. 10 (1):1-10.

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 *in vivo* metabolism of chloroform to phosgene ($COCl_2$) was confirmed by recent studies of Pohl et al. (1). Phenobarbital pretreated rats were treated with cysteine (1.0g/kg, intraperitoneally (i.p.), followed by $CHCl_3$ (4.98 mmole/kg, i.p.) 30 minutes later. Livers were removed after 1 hour and analyzed for $COCl_2$ as the cysteine conjugate and for 2-oxothiazolidine-4-carboxylic acid by gas chromatography-mass spectrometry. A fraction with the same retention time and mass spectrometry value as the synthetic standard was detected in the liver extract. The identification of the fraction as trapped $COCl_2$ was confirmed by repeating the experiment with ^{13}C-labeled $CHCl_3$.

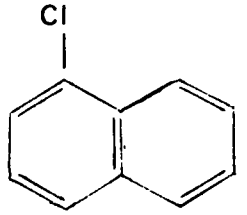
Reference

1. Pohl, L.R., J.W. George and G. Krishna. 1979. Phosgene: an *in vivo* metabolite of chloroform. *Toxicol. Appl. Pharmacol.* 48(1):A110. Abstr.

CHLORONAPHTHALENE

$C_{10}H_7Cl$

Mol wt: 162.62g/mole



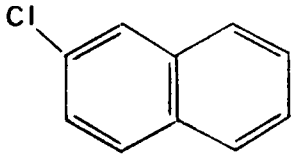
1-chloronaphthalene

CAS: 000090131

Syn: alpha-chloronaphthalene

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)

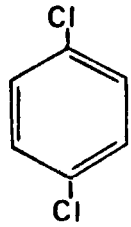
Chu et al. (1) studied the metabolism of 2,6-dichloronaphthalene. Rabbits were given a single dose of this compound (300 mg/kg) in 1% aqueous gum tragacanth. A dose of 1 g/kg was similarly given to 4 rats and their urine collected for one week. The three metabolites identified from the urine samples were: 6-chloro-2-naphthol, 7-chloro-2-naphthol, and 6-chloro-1-naphthol. More than 50% of the 2,6-dichloronaphthalene was recovered unchanged from the urine.

Reference

1. Chu, I., V. Secours and A. Vieau. 1976. Metabolites of chloronaphthalene. Chemosphere 5:439-444.

p-DICHLOROBENZENE

$C_6H_4Cl_2$



CAS: 000106467

Syn: p-dichlorobenzene; paradichlorobenzene; paradichlorobenzol

Mol wt: 147.01 g/mole

bp: 174°C (at 760 mm Hg)

vp: 1.1 mm Hg (at 30.0°C)

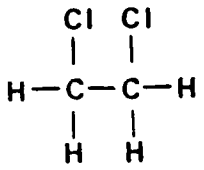
Kimura et al. (1) examined the levels of two metabolites of p-dichlorobenzene in blood and some other tissues (adipose, kidney, lung, liver, heart, and brain) as well as the excretion levels of these metabolites in urine and feces of treated rats. A dosage of 200 mg/kg of p-dichlorobenzene was administered orally to fasted male rats. The two metabolites identified by gas chromatography were 2,5-dichlorophenyl methyl sulfoxide (M-1) and 2,5-dichlorophenyl methyl sulfone (M-2). The initial concentrations of the sulfoxide (M-1) in the blood were initially higher than M-2 levels, but the level of M-2 persisted in the blood for up to 120 hours (compared to 70-80 hours for M-1). Of the organ tissues analyzed, the kidneys contained the highest concentration of M-1. However, the highest absolute concentrations of M-2 were found in blood samples. Excretion of M-1 and M-2 in urine and feces was less than .013% of the dosage administered.

Reference

1. Kimura, R., T. Hayashi, M. Sato, T. Aimoto and T. Murata. 1979. Identification of sulfur-containing metabolites of p-dichlorobenzene and their disposition in rats. J. Pharmacol. Dyn. 2:237-244.

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)

Kokarozetseva and Kiselea (1) recently reported the identification of two metabolites of 1,2-dichloroethane as monochloroacetic acid and chloroethanol. Albino rats were administered intragastrically a single dose of 750 mg/kg 1,2-dichloroethane. The authors pointed out that the metabolites are more toxic than the parent compound and may be considered an example of lethal synthesis.

Livesey and Anders (2) studied the in vitro metabolism of 1,2-dichloroethane to ethylene. Rat hepatic and renal enzymes were used as the in vitro system. The reaction was inhibited by p-dichloromercuribenzoate and diethylmaleate; whereas, cyanide, fluoride, or SKF 525A (B-diethylaminoethyldiphenyl propylacetate) did not inhibit metabolism.

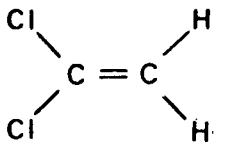
References

1. Kokarovtseva, M.G. and N.I. Kiseleva. 1978. Chloroethanol (ethylene chlorohydrin), one of the toxic metabolites of 1,2-dichloroethane. Farmakol Toksikol (Mosc) 41(1):118-120.

2. Livesey, J.C. and M.W. Anders. 1979. Glutathione-dependent metabolism of vicinal-dihalides to olefins. Pharmacologist 20 (3):187. Abstr.

1,1-DICHLOROETHYLENE

$C_2H_2Cl_2$



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)

Reichert and Werner (1) recently confirmed the previous findings of McKenna, Jaeger, and their co-workers that the rate of depletion of glutathione after oral doses of 1,1-dichloroethylene (1,1-DCE) was exponentially dependent on 1,1-DCE concentration. After 24-hour oral administration of a sublethal concentration of 1,1-DCE, glutathione returned to the baseline level. A similar steep decline in concentration was also observed in 18-hour fasted rats. The investigators fed 1000 mg/kg 1,1-DCE dissolved in 2 ml/kg olive oil to rats by stomach tube. After 4-hours, the concentration of glutathione dropped to approximately 30% of the control values. The conversion rate of 1,1-DCE to a metabolite by isolated perfused livers was recorded as 7.64 μmoles/g liver after 3-hours perfusion when 5000 ppm was supplied in the gas phase. The metabolite was not identified but the authors suggested it might be an unstable epoxide. No effect on viability nor on the metabolism rate was noted when the livers of 18-hour fasted rats were perfused. The concentrations of the glutamate-oxaloacetate transaminase (SGOT) and glutamate-pyruvate transaminase (SGPT) in the perfused rat livers failed to show an increase. The authors concluded that there was no correlation between the liver glutathione level and the increased lethality of 1,1-DCE in fasted rats.

McKenna et al. (2,3) found that fasted rats exposed to 200 ppm ^{14}C vinylidene chloride (1,1-DCE) sustained liver and kidney damage not observed in fed rats. The liver centriolobular damage involved hepatic necrosis. The elimination of nonvolatile urinary metabolites was slightly greater in fed rats, suggesting a reduced capacity for metabolism in the fasting condition. Four major urinary metabolites were separated by high pressure liquid chromatography. Two of the four metabolites were identified by gas chromatography-mass spectrometry as S-(2-hydroxyethyl)-N-acetyl-cysteine and thiodiglycolic acid. Both the hepatotoxic response to vinylidene chloride and the extent of its detoxification appeared to be dependent on the concentration of glutathione (GSH) in the liver. When hepatic GSH was depleted (i.e. in fasted rats or after high doses of vinylidene chloride), a toxic response was elicited.

Andersen et al. (4) reported that the toxic metabolites of 1,1-dichloroethylene reacted with hepatic glutathione and that pretreatment with epoxypropanol or styrene oxide increased the toxicity of these metabolites. In fasted male rats, epoxypropanol, cyclohexene oxide, and butadiene monoxide caused prolonged depletion of H-GSH. The 2 hour LC_{50}'s of rats pretreated with cyclohexene oxide, styrene oxide, and epoxypropanol were 569, 163, and 92 ppm, respectively. Epoxide-induced enhancement of toxicity depended primarily on the particular epoxide used and not solely on the depletion of H-GSH. (The toxic metabolites were not identified in the abstract.)

In a follow-up article, Andersen et al. (5) investigated the toxicity of the epoxidic metabolite of 1,1-dichloroethylene in fasted male rats. The epoxide metabolite of 1,1-DCE is unstable and these authors reported it has never been isolated. The two pathways of detoxification, i.e. reaction with glutathione (GSH) and enzymatic hydration, along with the acute toxicity of seven

of these epoxidic metabolites were compared. The seven epoxides tested were trichloropropane oxide (TCPO), styrene oxide (SO), cyclohexane oxide (CHO), 2,3-epoxypropan-1-ol (2,3-EP), epichlorhydrin (EPI), epoxypropane (EP), and butadiene monoxide (BMO) as well as the sulfhydryl depleting agent diethylmaleate (DEM). These were administered intraperitoneally to fasted male rats at LD_{50} levels established for each compound. BMO, SO, 2,3-EP, CHO, and DEM treatment resulted in virtually total depletion of hepatic GSH within 2 hours following administration. Pretreatment of the above compounds for two hours prior to exposure of 1,1-dichloroethylene resulted in increased toxicity levels (lowered LD_{50}'s) in the following order: 2,3-EP>DEM>EPI>SO>BMO>CHO. This exacerbation of 1,1-dichloroethylene toxicity is thought to be related to the ability of these compounds to decrease hepatic GSH. The authors concluded that epoxide-hydrating pathways appear to be of minimal significance in the metabolism of 1,1-dichloroethylene reactive intermediates.

References

1. Relchert, D., W.H. Werner and D. Henschler. 1978. Role of glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver. Arch. Toxicol. 41:169-178.

2. McKenna, M.J., J.A. Zemple, E.O. Madrin and P.J. Gehring. 1978. The pharmacokinetics of (^{14}C) vinylidene chloride in rats following inhalation exposure. Toxicol. Appl. Pharmacol. 45(2):599-610.

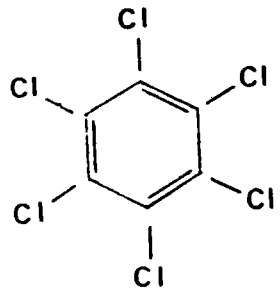
3. McKenna, M.J., J.A. Zempel, E.O. Madrin, W.H. Braun and P.J. Gehring. 1978. Metabolism and pharamacokinetic profile of vinylidene chloride in rats following oral administration. Toxicol. Appl. Pharmacol. 45(3):821-836.

4. Andersen, M., O. Thomas and L. Jenkings, Jr. 1979. Glutathione, epoxides and multiple detoxification pathways in the metabolism of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 48(1):A105. Abstr.

5. Andersen, M., O. Thomas, M. Gargas, R. Jones and L. Jenkings, Jr. 1980. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichlorethylene. Toxicol. Appl. Pharmacol. 52:422-432.

HEXACHLOROBENZENE

C_6Cl_6

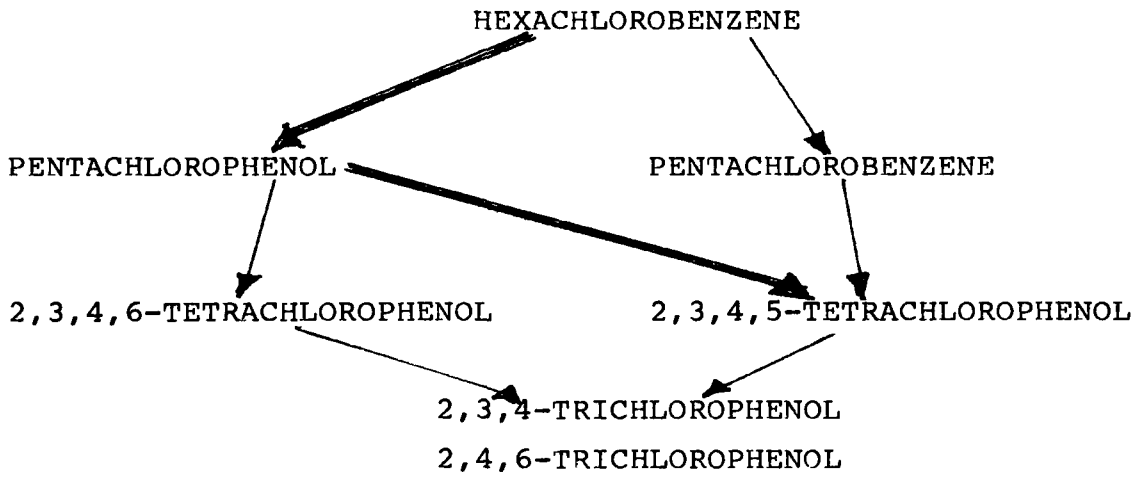


CAS: 118.74-1
Syn: HCB, Perchlorobenzene
Mol wt: 284.79 g/mole
bp: 322 (at 760 mm Hg)
vd: 9.84

Iatropoulos et al. (1) gave a single intragastric dose of 150 ug ^{14}C-labeled hexachlorobenzene to rats and examined the animals 1 to 48 hours later. Little hexachlorobenzene was absorbed during the first hour. After 5 hours, increasing concentrations of hexachlorobenzene were observed in the lining of the jejunum and ileum, with the highest amounts recorded in lymph and adipose tissues.

In another study, Mehendale et al. (2) gave a single oral dose of ^{14}C-labeled hexachlorobenzene to adult male rats. Approximately 16% of the dose was excreted in the feces and less than 1% in urine. Seventy percent of the hexachlorobenzene remained in the body 7 days after administration with adipose tissue fat being the major site of deposition. Reductive dechlorination of hexachlorobenzene was catalyzed by an enzyme located in the microsomal fraction of liver, lung, kidney, and intestine. Most of the studies on chlorinated benzenes have shown that the greater number of chlorine atoms the halogenated benzene contained, the less rapidly the compound is metabolized. Oxidative hydroxylation and reductive dechlorination have been shown to be the main routes of conversion in metabolic pathways of this compound.

Engst et al. (3) gavaged male rats daily with 8 mg hexachlorobenzene at a concentration of 8 mg/kg for 19 days. Pentachlorobenzene and pentachlorophenol were found at low concentrations in the organs and tissues of the treated animals. Urine collected from treated animals contained hexachlorobenzene and pentachlorophenol (the main metabolite) together with 2,3,4,6- and/or 2,3,4,5-tetrachlorophenol, 2,4,6-trichlorophenol, pentachlorobenzene, and traces of 2,3,4- and other trichlorophenols. Small amounts of the glucuronides of 2,4,6-trichlorophenol and 2,3,4,6-tetrachlorophenol were also present in the urine. The main degradation route for hexachlorobenzene in rats has been proposed by Engst (3). Pentachlorobenzene and its main metabolite 2,3,4,5-tetrachlorophenol were detectable at trace levels only.



DEGRADATION ROUTE FOR HEXACHLOROBENZENE

Engst et al. (3)

Koss et al. (4) gave female rats of ^{14}C-labeled hexachlorobenzene in 2 or 3 intraperitoneal injections over a period of 5 or 10 days to attain a total dose of 260 or 290 mg/kg. The mean excretion of labeled ^{14}C totalled 7% in the

urine and 27% in the feces. In the feces, about 30% of the excretory products labelled were in the form of metabolites and 70% as unchanged hexachlorobenzene. 90% of urinary labelled excretory products were in the form of metabolites, principally pentachlorophenol, tetrachlorohydroquinone, and pentachlorothiophenol. In the tissues, the only metabolite detected in measurable amounts was pentachlorophenol: 10% in blood, 3.5% in liver, 2% in kidney, 1% in brain, and 0.1% in body fat.

In 1978, Rozman et al. (5) reported the pharmacokinetics of hexachlorobenzene in rhesus monkeys Macaca mulatta. The animals were fed a diet containing 1 ppm ^{14}C-labeled hexachlorobenzene for 18 months. The radioactive products excreted in the feces were: 99% as hexachlorobenzene, 1% as pentachlorobenzene, and a trace of pentachlorophenol. The major urinary metabolite was pentachlorophenol. Other urinary metabolites identified were pentachlorobenzene, tetrachlorobenzene, and hexachlorobenzene. The only metabolite identified in the plasma was hexachlorobenzene. In the red blood cells, the metabolites identified were 95% hexachlorobenzene and about 5% pentachlorophenol. According to the authors, none of the monitored parameters indicated harmful effects to the rhesus monkey from a 110 µg/day (1 ppm) hexachlorobenzene-exposure over a period of 550 days.

Koss et al. (6) have recently reported the presence of sulphur-containing metabolites of hexachlorobenzene in rat excretion. The rats received oral doses of 178 µmoles/kg hexachlorobenzene. They identified pentachlorothiophenol and pentachloroanisole in the livers of animals treated with hexachlorobenzene. The metabolites of pentachlorothiophenol and pentachlorothioanisole were excreted in both conjugated and free forms. The extracts of the excreta of treated rats yielded tetra- and trichlorobenzene with two or three S-containing substitutions on the ring. Following administration of the

sulphoxide and of the sulphone of pentachlorothionanisole under analogous conditions, pentachlorothioanisole and pentachlorothiophenol and their metabolites were detected in the excreta of the test animals.

References

1. Iatropoulos, M.J. 1975. Absorption, transport and organotropism of dichlorobiphenyl (DCB), dieldrin, and hexachlorobenzene (HCB) in rats. Environ. Res. 10:384-389.

2. Mehendale, H.M., M. Fields and H.B. Matthews. 1975. Metabolism and effects of hexachlorobenzene on hepatic microsomal enzymes in the rat. J. Agric. Food Chem. 23(2):261-265.

3. Engst, R., R.M. Machloz and M. Kujawa. 1976. The metabolism of hexachlorobenzene (HCB) in rats. Bull. Environ. Contam. Toxicol. 16(2):248-252.

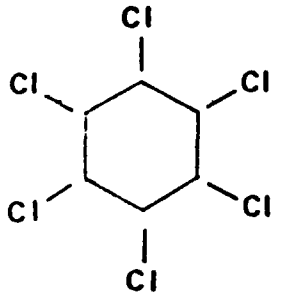
4. Koss, G., W. Koransky and K. Steinbach. 1976. Studies on the toxicity of HCB II: identification of metabolites. Arch. Toxicol. 35(2):107-114.

5. Rozman, K., W.F. Miller, F. Coulston and F. Korte. 1978. Chronic low dose exposure of rhesus monkeys to hexachlorobenzene (HCB). Chemosphere 7(2):177-184.

6. Koss, G., W. Koransky and K. Steinbach. 1979. Studies on the toxicology of hexachlorobenzene IV: sulfur-containing metabolites. Arch. Toxicol. 42(1):19-31.

LINDANE

$C_6H_2Cl_6$



CAS: 58-89-9

Syn: gamma-Hexachlorocyclohexane, gamma-1,2,3,4,5,6-Hexachlorocyclohexane, gamma HCH, HCH

Mol wt: 290.83 g/mole

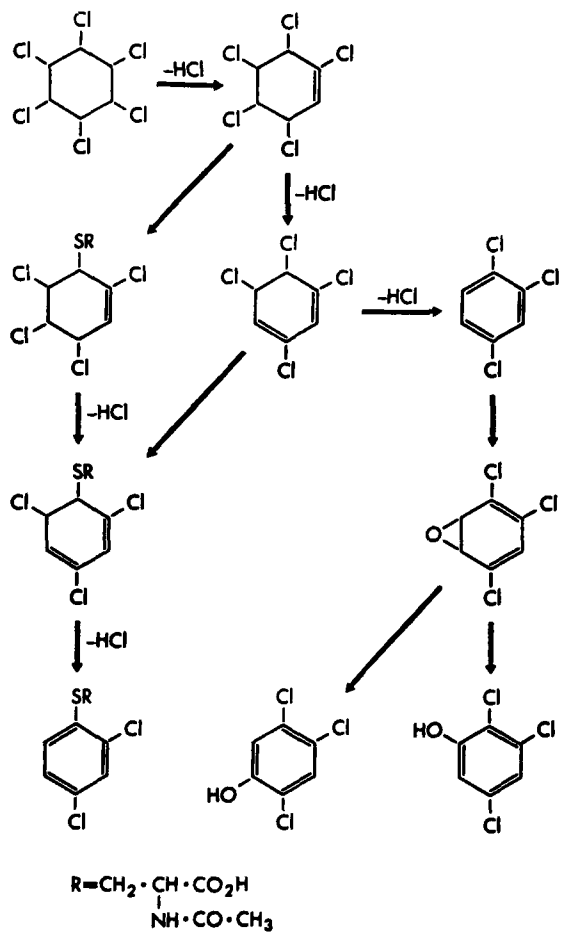
bp: 288°C (at 760 mm Hg)

vp: .14 mm Hg (40° C)

Karapally et al. (1) examined the ether-soluble urinary metabolites of lindane in rabbits. ^{14}C lindane was fed to rabbits in gelatin capsules over a period of 26 weeks. 54% of the labeled lindane was excreted in the urine and 13% in the feces of the test animals. The following ether-soluble urinary metabolites were identified by infrared spectrometry: 2,3,5-, 2,4,5-, and 2,4,6-trichlorophenol and 2,3,4,6-tetrachlorophenol. Other metabolites identified by gas chromatography were: 2,3- and 2,4-dichlorophenol and 2,3,4,5-tetrachlorophenol. Tentative identification was made by gas chromatography of seven other chlorophenols and six chlorobenzenes: 2,5-, 2,6-, and 3,4-dichlorophenol, 2,3,4-, 2,3,6-, and 3,4,5-trichlorophenol, pentachlorophenol, 1,2-dichlorobenzene, 1,2,4 trichlorobenzene, 1,2,3,4-, 1,2,4,5-, and/or 1,2,3,5-tetrachlorobenzene, and pentachlorobenzene.

In another article, Chadwick and Freal (2) identified five unreported lindane metabolites in rat urine. Rats were fed diets of 400 ppm lindane and their urine was collected. The following metabolites were identified by gas chromatography and/or infrared spectrometry: 3,4-dichlorophenol, 2,4,6-trichlorophenol, 2,3,4,5-tetrachlorophenol, 2,3,4,6-tetrachlorophenol, and 2,3,4,5,6-pentachloro-2-cyclohexen-1-ol. In addition, the

previously identified metabolites 2,3,5- and 2,4,5-trichlorophenol were also identified in this study. The following lindane metabolic pathway was also included in this article. Lindane is dehydrochlorinated to ϑ pentachlorocyclohexane which is further metabolized to either 2,4-dichlorophenyl mercapturic acid or 2,3,5- and 2,4,5-trichlorophenol.



THE LINDANE METABOLIC PATHWAY PROPOSED BY GROVER AND SIMS Chadwick and Freal (2).

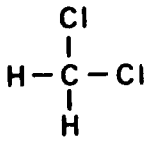
References

1. Karapally, J., J. Saha and Y. Lee. 1973. Metabolism of lindane-^{14}C in the rabbit: ether-soluble urinary metabolites. J. Appl. Food Chem. 21(5):811-817.

2. Chadwick, R.W. and J.J. Freal. 1972. The identification of five unreported lindane metabolites recovered from rat urine. Bull. Environ. Contam. Toxicol 7:137-146.

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)

Recently, the pharmacokinetics and metabolism of inhaled ^{14}C-methylene chloride (CH_2Cl_2) were studied by McKenna et al. (1). Rats were exposed one time only to 50, 500, or 1500 ppm for 6 hours. The two major metabolites found in the exhaled air were ^{14}CO and $^{14}CO_2$. The net uptake and rate of metabolism was not proportional to the increase in dosage. The relationship of total $^{14}CH_2Cl_2$ metabolism relative to exposure concentration followed the model of Michaelis-Menten kinetics. This model can be used to predict the body burden of CH_2Cl_2 in inhalation exposure.

Hake (2) examined the uptake by hemoglobin of CO derived from CH_2Cl_2. Its subsequent release into breath was measured by computer-predicted blood carboxyhemoglobin levels which are reached when a physically active worker is exposed to vapors. Simulated values of CH_2Cl_2 in breath and blood carboxyhemoglobin were first compared with experimental values obtained from sedentary humans previously exposed in the laboratory. When increased ventilation and cardiac output values were applied to

the simulated exposures at 50, 100, 250, and 500 ppm for 3 and 7.5 hours, blood carboxyhemoglobin levels did not increase proportionally to uptake. At 500 ppm exposure, simulated carboxyhemoglobin values were higher without exercise than with exercise.

In another study on the increased uptake by hemoglobin of CO derived from methylene chloride, Stewart and Hake (3) examined the possible complications in persons with cardiovascular problems resulting from inhalation of paint-remover vapors. Many paint removers contain up to 80% methylene chloride. Exposure of human volunteers to paint remover vapors at a range of exposure from 77-186 ppm methylene chloride under limited ventilation conditions for periods of three hours resulted in 5-10% COHb saturation. In heavy smokers, the levels were even higher since a heavy smoker can have up to a 10% saturation of COHb due to smoking alone. More physically active persons exhibited higher levels of COHb as a result of absorbing larger quantities of methylene chloride in the bloodstream. Since it has been shown by other studies that COHb levels of 5-10% can adversely affect patients with cardiovascular disease or angina pectoris, these researchers pointed out the potential danger of the use of paint removers by such individuals.

Peterson (4) exposed eleven men to methylene chloride (dichloromethane) concentrations of 50, 100, 250, and 500 ppm and nine women to a concentration of 250 ppm for up to five successive days. It has long been known that this material is converted to carbon monoxide endogenously. The author devised equations by which breath concentration of the solvent as well as the blood concentration of the metabolite carbon monoxyhemoglobin (COHb) following exposure were related mathematically to exposure parameters. The resulting empirical equations of this study can be used to predict the consequences of many industrial and non-industrial exposure situations. The author recommended that these equations be used for interpolation only and not for

extrapolation. The equations were valid for exposures to concentrations above 50 or below 500 ppm, for durations less than 1 hour or more than 7.5 hours, or for not more than 5 successive days of exposure. COHb level elevations of up to 10% saturation following inhalation exposure to methylene chloride were predicted by these equations using a knowledge of exposure parameters. Measurement of the breath concentration in the 24 hour period following exposure allowed for calculation of the duration of exposure, the number of successive exposure days, and the time-weighted average concentration inhaled during the exposure.

Reference

1. McKenna, M.J.. J.A. Zempel and WH. Braun. 1979. The pharmacokinetics and metabolism of inhaled methylene chloride in rats. Toxicol. Appl. Pharmacol. 48(1,pt.2):A10. Abstr.

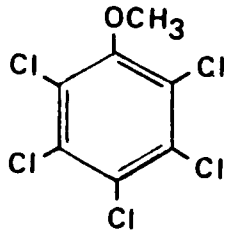
2. Hake, C.L. 1979. Simulation studies of blood carboxyhemoglobin levels associated with inhalation exposure to methylene chloride. Toxicol. Appl. Pharmacol. 48(1):A56. Abstr.

3. Stewart, Richard D. and Carl L. Hake. 1976. Paint-remover hazard. JAMA 235(4):398-401.

4. Peterson, Jack E. 1978. Modeling the uptake and excretion of dichloromethane by man. Amer. Ind. Hyg Assoc. J. 39:41-47.

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

bp: 289° (at 745 mm)

vp:

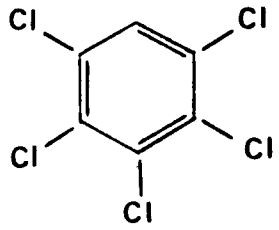
Pentachloroanisole is a major degradation product of pentachlorophenol as reported by Pierce and Victor (1). They studied the fate of pentachlorophenol in aquatic ecosystems where its accidental release had caused extensive fish kills. Other degradation products of pentachlorophenol identified in this study were 2,3,5,6- and 2,3,4,5-tetrachlorophenol isomers. These products persisted in fish and in sediment for up to 2 years. The investigators suggested the formation of pentachloroanisole in water whereas tetrachlorophenol appeared to be formed by photodegradation before entering the lake.

Reference

1. Pierce, R.H., Jr., and D.M. Victor. 1978. The fate of pentachlorophenol in an aquatic ecosystem. Env. Sci. Res. 12 (Pentachlorophenol): Chem. Pharmacal. Environ. Toxicol:41-52.

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)

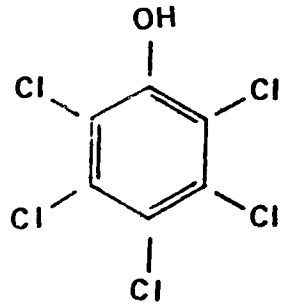
Recently, Rozman et al. (1) reported the metabolism of pentachlorobenzene in rhesus monkeys. The animals were orally administered ^{14}C-labeled pentachlorobenzene (0.5 mg/kg) in a single dose. Several blood samples were taken within 40 days following treatment. Two monkeys (one male, one female) were then sacrificed. At least 95% of the compound was absorbed as indicated by fecal excretion in the first 4 days. About twice the compound level was present in feces as was present in urine. The half-life of pentachlorobenzene in rhesus monkey was estimated to be 2 to 3 months. The level of pentachlorobenzene in blood peaked between 2 and 4.5 hours. The highest concentrations of pentachlorobenzene occurred in fat and bone marrow, followed by decreasing concentrations in the lymph nodes, thymus, adrenal cortex, and large intestine. The metabolites of pentachlorobenzene identified were: pentachlorophenol, 2,3,4,5-tetrachlorophenol, 2,3,5,6-tetrachlorophenol, and 1,2,3,4-tetrachlorobenzene. The authors did not find any significant difference in metabolism patterns between male and female monkeys. They also postulated that in addition to hepatic cytochrome P-450, there may exist an additional metabolic pathway which involves the hyroxylation of higher chlorinated benzenes.

Reference

1. Rozman, K., J. Williams, W.F. Miller, F. Coulston and F. Kate. 1979. Metabolism and pharmacokinetics of pentachlorobenzene in the rhesus monkey. Bull. Environ. Contam. Toxicol. 22(1-2):190-195.

PENTACHLOROPHENOL

C_6Cl_5OH



Cas: E 7-86-5
Syn: PCP, Penchlorol
Mol wt: 266.34 g/mole
bp: 309.10
vp: .00011 mm (at 20°C)

Ahlborg et al. (1) studied the metabolism of pentachlorophenol (PCP). Rats and mice were administered 10-25 mg/kg pentachlorophenol either intraperitoneally or orally. Excretion of PCP in the urine of test animals was measured by gas chromatography-mass spectrometry. 43-44% of the excretion products were unchanged PCP. The metabolite tetrachlorohydroquinone represented 5-24% of excreted products. This metabolite has also been reported in the urine of occupationally exposed workers.

In a follow-up report, Ahlborg et al. (2) addressed the *in vivo* and *in vitro* metabolism of PCP to tetrachloro-p-hydroquinone in rats and rat microsomal incubate, respectively. The rats were pretreated with phenobarbital (PB) and SKF-525A (B-diethylaminoethyldiphenyl propylacetate). The *in vivo* rats were administered PB or SKF-525A intraperitoneally (i.p.) for three consecutive days. On the fourth day, PCP was injected i.p. at 10 mg/kg. The urine was collected and analyzed by gas chromatography-mass spectrometry. In the *in vitro* experiment, the rats were pretreated for five consecutive days with PB or SKF-525A i.p., sacrificed, and the liver microsomal incubate prepared. The microsomal incubate was treated with PCP dissolved in acetone. PB pretreatment increased the metabolism of PCP to

tetrachloro-p-hydroquinone in both cases. SKF-525A inhibited *in vitro* metabolism, but enhanced *in vivo* metabolism if given less frequently than every six hours.

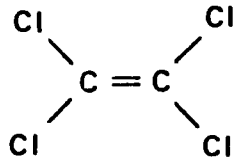
References

1. Ahlborg, U.G., J.E. Lindgren and M. Mercier. 1974. Metabolism of pentachlorophenol. *Arch. Toxicol.* 32:271-281.

2. Ahlborg, U.S., K. Larsson and T. Thunberg. 1978. Metabolism of pentachlorophenol *in vivo* and *in vitro*. *Arch Toxicol.* 40(1):45-53.

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)

Pegg et al. (1) administered ^{14}C-tetrachloroethylene to rats orally (1 or 500 mg/kg) or by inhalation (10 or 600 ppm, for 6 hours). Following a 1 mg/kg oral dose or inhalation of 10 ppm ^{14}C-tetrachloroethylene, approximately 70% of the radioactivity was excreted (as ^{14}C-tetrachloroethylene) in expired air, 26% as ^{14}CO nonvolatile metabolite in urine and feces, and 3 to 4% remained in the carcasses. After oral administration of 500 mg/kg or inhalation of 600 ppm of ^{14}C tetrachloroethylene, 89% of radioactivity was recovered as tetrachlorethylene in expired air, 9% as urinary and fecal metabolites, and 1 to 2% remained in the carcasses. The authors estimated the half-life of tetrachloroethylene to be 7 hours irrespective of dose or route of administration. The radioactivity in the carcasses was mainly concentrated liver, kidney, and adipose tissue. Exposure to 600 ppm tetrachloroethylene vapor 6 hours per day, 5 days a week for 12 months did not result in organ toxicity.

Monster et al. (2) recently reported their investigations of six male volunteers exposed for 4 hours to a range of concentrations of 72 and 144 ppm tetrachloroethylene while at

rest and to 142 ppm combined with exercise. The uptake dropped to 60% during the initial exposure and was influenced more by lean body mass than by respiratory volume or adipose tissue. One notable feature was a three- to four-fold increase in uptake during exercise. Approximately 80 to 100% of the uptake was excreted unchanged by the lungs after exposure. After 70 hours of exposure, the amount of trichloroacetic acid excreted in urine was approximately 1% of the uptake.

Hake and Stewart (3) reported several documented cases of accidental human exposure of tetrachloroethylene through skin contact and/or inhalation. In these cases of accidental human exposure, the narcotic effects as well as the liver and kidney damage suffered by the victims appeared reversible. In controlled inhalation studies carried out by the authors as well as other researchers, factors such as the levels of physical activity, individual metabolic differences, and length and concentration of exposure were found to be critical factors in determining individual reactions to tetrachloroethylene exposure. Light exercise increased the blood levels up to four-fold after 30 min. of moderate exercise during 100 ppm exposure. Alcohol and valium did not affect blood levels. In general, the authors felt that exposures of 100 ppm tetrachloroethylene normally does not pose a serious health threat. However, due to individual differences in metabolism and different levels of physical activity during individual exposures, the authors suggested that the determination of body burden of this chemical in individuals exposed in the workplace would be advisable.

References

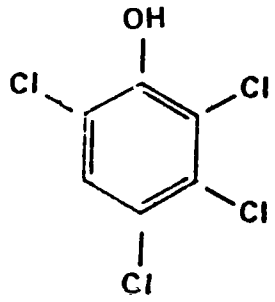
1. Pegg, D.G., J.A. Zempel, W.H. Braun and P.J. Gehring. 1978. Disposition of [^{14}C] tetrachloroethylene following oral and inhalation exposure in rats. Toxicol. Appl. Pharmacol. 45(1):276-77.

2. Monster, A.C., G. Boersma and H. Steenweg. 1979. Kinetics of tetrachloroethylene in volunteers: influence of exposure concentration and work load. Int. Occup. Environ. Health. 42(3-4):303-309.

3. Hake, C.L. and R.D. Stewart. 1977. Human exposure to tetrachloroethylene: inhalation and skin contact. Environ. Hlth. Perspect. (21):231-238.

TETRACHLOROPHENOL

$C_6H_2Cl_4O$



2,3,4,6-tetrachlorophenol isomer

CAS: 25167-83-3
Syn:
Mol. wt: 231.9 g/mole
bp: 164°C (at 23mm)
vp: 60 mm (at 190°C); 400 mm (at 250°C)

Tetrachlorophenols are used as fungicides and they have been reported as mammalian metabolites of gamma-benzenehexachloride (lindane) in rats (1), and rabbits (2). (See "Lindane" section for further details of these articles).

Jondorf et al. (3) reported tetrachlorophenol as a metabolite of tetrachlorobenzene in the urine of doe chinchilla rabbits. The test animals were administered tetrachlorobenzene by stomach tube or subcutaneously in a 10% solution. The urine was collected and was analyzed by mass spectrometry and by paper chromatography.

Ahlborg and Larsson (4) studied the metabolism of tetrachlorophenols in rats. Three isomers of tetrachlorophenol were adminstered intraperitoneally to rats. During the first 24 hours, the rats excreted tetrachloro-p-hydroquinone as a major urinary metabolite of 2,3,4,6-tetrachlorophenol (about 35% of the given dose). Trichloro-p-hydroquinone was considered as a minor urinary metabolite of both 2,3,4,5- and 2,3,4,6-tetrachlorophenols. Only 60% of the given dose of 2,3,4,5-tetrachlorophenol was recovered within 72 hours while 2,3,4,6-tetrachlorophenol was eliminated in the urine of treated animals within 48 hours. The metabolites were identified by gas chromatography.

References

1. Chadwick, R.W., and J.J. Freal. 1972. The identification of five unreported lindane metabolites recovered from rat urine. Bull Environ. Contam. Toxicol. 7:137-146.

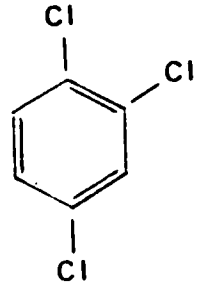
2. Karapally, J.C., J.G. Saha, and Y.W. Lee. 1973. Metabolism of lindane ^{14}C in the rabbit: ether-soluble metabolites. J. Agri. Food Chem. 21:811-818.

3. Jondorf, W.R., D.V. Parke and R.T. Williams. 1958. Studies in detoxification. 76. The metabolism of halogenobenzenes: 1:2:3:4-, 1:2:3:5- and 1:2:4:5:-tetrachlorobenzenes. Biochem. J. 69(2):181-189.

4. Ahlborg, U.G. and K. Larsson. 1978. Metabolism of tetrachlorophenols in the rat. Arch. Toxicol. 40(1):63-74.

1,2,4-TRICHLOROBENZENE

$C_6H_3Cl_3$



CAS: 000120821
Syn: unsym-trichlorobenzene
Mol wt: 181.45 g/mole
bp: 213.5°C (at 760 mm Hg): 84.8°C at 10 mm Hg)
vp: 1.04 mm Hg (at 38.4°C)

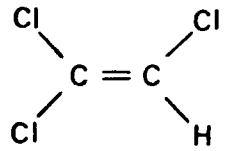
Recently, the uptake and elimination kinetics and biotransformation of trichlorobenzene were studied in rainbow trout (1). The fish were exposed to aqueous trichlorobenzene in static systems for short exposure conditions and continuous flow delivery for long exposure conditions. The results were evaluated by a computer program (BIOFAC). Bioconcentration factors of approximately 100 were achieved from an 8 hour exposure (0.02 mg/ml). A four day exposure (.001 and .01 mg/ml) gave a bioconcentration factor of approximately 400. Trout bile, which was exposed to 0.25 mg/ml trichlorobenzene for 24 hour contained 5 mg/ml of the parent compound and 10 mg/ml of biotransformation products. Muscle and liver extracts contained 0.8% and 3.7% biotransformation products, respectively. (The biotransformation products were not identified in the abstract.)

Reference

1. Melancon Jr., M.J., D.R. Branson and J.J. Lech. 1979. The uptake elimination and metabolism of 1,2,4-trichlorobenzene in rainbow trout. Toxicol. & Appl. Pharmacol. 48(1):A170. Abstr.

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 (at 25°C)

Relative to interactions between trichloroethylene and ethanol, Stewart et al. (1) investigated the role of trichloroethylene (TCE) in eliciting "degreasers flush." This phenomenon has been observed in workers constantly exposed to trichloroethylene in the workplace who visited neighborhood taverns to drink beer. This is a dermal response in many of these workers of vivid red symmetrical blotches on the face, neck, shoulders, and back. To establish the role of TCE in this phenomenon, these researchers exposed seven male volunteers to TCE vapors at levels of 20, 100, and 200 ppm for varying periods of 1-7½ hours. Dosages of ethanol (less than 0.5 ml/kg body weight) were then ingested by the volunteers. In six of the seven volunteers tested, the dermal response occurred after three weeks of the first TCE exposure. This led the investigators to speculate that a metabolite of TCE rather than the TCE itself must reach a threshold level to elicit the dermal response. However, the metabolite was not identified.

The metabolism, uptake, and elimination rates in humans of trichloroethylene, 1,1,1-trichloroethane, and tetrachloroethylene were compared recently by Monster (2). He found that

trichloroethylene was absorbed almost constantly at a relatively higher rate than the other compounds due to its high partition coefficient between blood and air resulting in rapid metabolism of trichloroethylene. Although the partition coefficient between blood and air of tetrachloroethylene was about the same as trichloroethylene, the metabolism of tetrachloroethylene was less complete. Only a relatively small amount of trichloroethylene was shown to be excreted by the lungs.

In a follow-up study, the same authors (3) exposed 5 male volunteers to 70 ppm trichloroethylene for 4 hours inhalation on 5 consecutive days. The uptake of this compound in lean body mass was 6.6 mg/kg within 4 days. Eighteen hours after the 5th day of exposure, the amount of trichloroethylene in exhaled air and in blood was twice the level of the first exposure. The amount of trichloroethanol excreted within a 24-hour period increased from an average of 142 mg (1st day) to 217 mg (5th day) which indicated a diurnal rhythm. The total amount of trichloroethylene recovery was 78%: 11% was unchanged, 43% as trichloroethanol, and 24% as trichloroacetic acid. There was a correlation between the lean body mass and trichloroethanol alone and trichloroethanol with trichloroacetic acid excreted in urine. The authors considered trichloroacetic acid in blood to be a good monitoring parameter due to the minimal interindividual variation.

Monster and Houtkooper (4) further reported a method for estimating human uptake of trichloroethylene, methylchloroform, and tetrachloroethylene from the concentrations of solvents and metabolites in biological media at 2 and 20 hours after a single exposure. The method involved simple linear and multiple regression analyses. The best results were obtained by estimations from the concentrations in blood, particularly of the solvents themselves.

In another study, Hathway (5) reported the presence of two chloral metabolites in the urine of 5-week-old male rats in which 1,1,2-trichloroethylene (stabilized with 0.02% triethylamine) was administered intragastrically at a level of 2.0 ml/kg. The treated and the control animals were housed in glass metabolism cages to collect urine and fecal samples. Analysis of the urine of treated mice by gas chromatography-mass spectrometry demonstrated the presence of trichloroacetic acid and a small amount of dichloroacetic acid. These metabolites were not detected in the urine of control animals. Dichloroacetic acid is not thought to be formed in 1,1,2-trichloroethylene metabolism in mammals other than mice and may be responsible for oncogenicity in treated mice. The researcher proposed that the rearrangement of 1,1,2-trichloroethylene oxide into chloral and its metabolic products rather than into dichloroacetic acid is the possible reason for the relative harmlessness of exposure to 1,1,2-trichloroethylene in rats and man.

Ogata et al. (6) studied urinary excretion of trichloroethylene in rabbits, rats, and mice. Levels of the metabolites of trichloroethylene (trichloroethanol and trichloroacetic acid) were determined by gas chromatography in the urine of animals injected with 1 mmole/kg trichloroethylene. The ratio of total excretion of these metabolites to the total dosage, as well as the ratio of trichloroethanol to trichloroacetic acid, varied among the three test species.

Ogata and Yamazaki (7) reported the development of a liquid chromatographic method for the determination of trichloroacetic acid levels in urine as a index of trichloroethylene exposure. With this method, urine can be analyzed within ten minutes without pretreatment or solvent extraction at a minimal detection limit of 0.5 μg.

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16. ABSTRACT

This is the first update to an earlier EPA report entitled "Metabolism Summaries of Selected Halogenated Organic Compounds in Human and Environmental Media, A Literature Survey" (EPA-560/6-79-008). This update provides additional information on fifteen halocarbons covered in the original report as well as information on four new halocarbons. As did the earlier literature summary, this update deals with the uptake, retention, distribution and elimination patterns, identification of metabolites, and metabolic pathways of the halocarbons.

17. KEY WORDS AND DOCUMENT ANALYSIS

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

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