

**NIOH and NIOSH basis for an occupational
health standard**

Chlorobenzene



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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National Institute for Occupational Safety and Health



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NIOH and NIOSH Basis for an Occupational Health Standard:

Chlorobenzene

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PREFACE

A memorandum of understanding has been signed by two government agencies in the United States and Sweden—the Division of Standards Development and Technology Transfer of the National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services (DSDTT/NIOSH), and the Criteria Group of Occupational Standard Setting, National Institute of Occupational Health (NIOH) (formerly Research Department of the National Board of Occupational Safety and Health). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide the scientific basis for establishing occupational exposure limits. These limits will be developed separately by the two countries according to their different national policies.

This document on the health effects of occupational exposure to chlorobenzene is the fifth product of that agreement. This document was written by Dr. Björn Hellman, Department of Occupational Medicine, University Hospital, Uppsala, Sweden, and was reviewed by the Criteria Group and by DSDTT/NIOSH.

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ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ALAT	serum alanine aminotransferase
ASAT	serum aspartate aminotransferase
BUA	Beratergremium für umweltrelevante Altstoffe der Gesellschaft Deutscher Chemiker (Germany)
b.wt.	body weight
CNS	central nervous system
DNA	deoxyribonucleic acid
EPA	U.S. Environmental Protection Agency
GC	gas chromatography
GSH	reduced glutathione
GSSG	oxidized glutathione
HD	highest dose group
HPLC	high performance liquid chromatography
IBT	International Bio-Test Inc. (USA)
IARC	International Agency for Research on Cancer
i.p.	intraperitoneal (injection)
i.v.	intravenous (injection)
LC ₅₀	the concentration (in air or water) needed to produce death in 50 percent of exposed animals; in the present document LC ₅₀ refers to inhalation concentration
LD ₅₀	the dose of chemical needed to produce death in 50 percent of dosed animals
LOEL	lowest observed effect level
m-	meta- (positions 1,3- in a disubstituted ring structure)
MD	medium dose group
NIOH	National Institute of Occupational Health (Sweden)
NIOSH	National Institute for Occupational Safety and Health (USA)

NOAEL	no observed adverse effect level
NOEL	no observed effect level
NTP	National Toxicology Program (USA)
o-	ortho- (positions 1,2- in a disubstituted ring structure)
OSHA	Occupational Safety and Health Administration (USA)
p-	para- (positions 1,4- in a disubstituted ring structure)
ppm	parts per million
RNA	ribonucleic acid
SCEs	sister chromatid exchanges
SKF 525-A	β -diethylaminoethyl diphenylpropyl acetate
TLV	threshold limit value (relates to concentration in air at workplaces)
TWA	time-weighted average exposure

1 INTRODUCTION

Chlorobenzene is one of twelve possible chemical species in the group of chlorinated benzenes (36). At room temperature, the substance is a colorless volatile liquid with an odor that has been described as “not unpleasant” (63), like that of “mothballs or benzene” (25) and “almondlike” (1, 32). The compound has been used extensively in industry for several years and its main use is as a solvent and intermediate in the production of other chemicals (19, 25, 32). In occupational settings, the main exposure is from inhalation of the volatile compound.


The present document summarizes and evaluates information that has been considered most relevant for the assessment of the potential adverse health effects from occupational exposure to chlorobenzene. To achieve this objective, a literature search was performed in different biomedical and toxicological databases (e.g., in Medline; Cancerlit; Toxline; Excerpta Medica; National Technical Information Service; Healthline and Chemical Safety Newsbase) before the assessment was initiated (July, 1991).

The U.S. Environmental Protection Agency (EPA) has recently prepared a health effects criteria document (final draft) for chlorobenzene (32) as well as an updated health effects assessment (33). A similar document has also been prepared in Germany (19). These, and other reviews (e.g., 2, 6, 25, 68, 92), have been included among the references in the present document.

The various health criteria documents mentioned above have included information from several unpublished toxicity studies, mainly performed by, or on behalf of, various manufacturers of chlorobenzene. Some unpublished investigations are also cited in the present document, although the primary sources of information often were unavailable for critical examination. In such a case, this has been indicated with a short remark, provided with the citation.

2 PHYSICAL AND CHEMICAL PROPERTIES

If not stated otherwise, the data on the physical and chemical properties of chlorobenzene were obtained from various reference books and review articles (1, 6, 7, 15, 19, 25, 26, 32, 63). Although not always declared, it is assumed that the figures given refer to chlorobenzene of analytical quality. Only scarce information on amounts and identities of potential impurities was available. In a teratogenicity study on rats and rabbits (48) using >99.9% pure chlorobenzene, it was stated that incidental impurities found consisted of benzene (<0.005%), bromobenzene (0.018%) and water (0.0077%). Chlorobenzene of technical quality from one of the German manufacturers is at least 99.8% pure, containing at most 0.06% dichlorobenzenes and 0.08% benzene, as the major impurities (19).

Chemical name:	Chlorobenzene
CAS number:	108-90-7
Synonyms:	Monochlorobenzene; MCB; monochlorbenzene; benzene chloride; benzene monochloride; chlorbenzene; CB; chlorbenzol; phenyl chloride
Physical state at room temperature:	Colorless, neutral liquid
Molecular formula:	C ₆ H ₅ Cl
Structural formula:	
Molecular weight:	112.56
Boiling point [101.3 kPa]:	13-132°C
Melting point:	-44.9°C [in ref. (6): -45.6°C]

Solidification (freezing) point:	-55°C
Flash point:	28°C
Vapor pressure [25°C]:	11.8 mm Hg = 15.81 hPa (25°C) 8.8 mm Hg = 11.73 hPa (20°C)
Saturation concentration in air [25°C]:	1.55% (15,526 ppm)
Vapor density [25°C]: (air = 1)	3.88
Specific density (gravity) [20°C; 25°C]:	1.107
Refractive index [25°C]:	1.5216
Solubility in water:	Practically insoluble (0.049 g/100 ml; 20°C)
Solubility in organic solvents:	Freely soluble in alcohol, benzene, chloroform, diethyl ether
Partition coefficient n-octanol/water:	log P _{ow} : 2.84 (58)
Other partition coefficients:	Water/air: 4.1 (79) Olive oil/air: 3,763 (79) Olive oil/water: 918 (79) Blood/air: 30.8 (71, 79)
Odor threshold: (see comments below)	In air: 0.21-0.68 ppm In water: 0.4-50 µg/l
Conversion factors [25°C; 101.3 kPa]:	1 ppm = 4.60 mg/m ³ 1 mg/m ³ = 0.217 ppm

The information on human thresholds for the detection of chlorobenzene is not uniform. In air, the recognition odor has been reported to vary between 0.21 ppm (7) and 0.68 ppm (3, 92) (i.e., between 1 and 3.1 mg/m³). However, in another source of information (91) it is stated that the almondlike odor of chlorobenzene is barely perceptible at 60 ppm (276 mg/m³). The air-dilution threshold given by Amoores and Hautala (3), 0.68 ppm, represents the geometric average of all available literature data, omitting extreme points and duplicate quotations.

The substance is practically insoluble in water, but the two liquids form an azeotrope that boils at 90°C (32). On surface water, chlorobenzene is believed to evaporate rapidly to the air. However, due to its greater density, chlorobenzene may also sink to the bottom of still volumes of water (32, 39). The reported taste/odor thresholds in water varies between 0.45–1.5 µg/l (this interval is based on the work by Tarkhova from 1965, cited in references 6 and 32) and 10–20 µg/l (based on the work by Varshavskaya from 1967, cited in references 6 and 32), respectively. However, these figures were considered difficult to interpret since none of the citations described the experimental conditions employed (32). In another, more recent work, the odor threshold for chlorobenzene in water was reported to be 50 µg/l (3). This so-called water-dilution odor threshold value was calculated from the concentration of the substance in water that would generate the air odor threshold (estimated to 0.68 ppm) in the headspace of a stoppered flask.

3 USES AND OCCURRENCE

The figures given below for production volumes, ambient air levels, etc., have mainly been obtained from secondary sources of information (6, 19, 32, 36, 49). Consequently, the original sources, often unpublished information, have generally not been evaluated in detail.

3.1 Production and Uses

Like other chlorinated benzenes, monochlorobenzene is commercially produced by the chlorination of benzene at an elevated temperature. This is done in the presence of a chlorination catalyst such as ferric chloride (36, 39, 63). Chlorobenzene may also be produced by treating phenol with aqueous sodium hydroxide under high pressure and in the presence of chloride (39).

Chlorobenzene is one of the most widely used chlorinated benzenes and it has been the dominant commercial isomer for at least 50 years. The compound has been utilized in numerous processes. Previously, its main uses were as a chemical intermediate in the synthesis of DDT and other organochlorine pesticides, and in the production of phenol and aniline (36, 92). During the first world war, it was also used in large quantities in the production of picric acid, which was utilized as an explosive (92). Its principal use today is as a chemical intermediate in the production of chemicals such as nitrochlorobenzenes and diphenyl oxide (19, 32, 36). In 1989, 76% of the total amount of chlorobenzene manufactured in the Federal Republic of Germany was processed into nitrochlorobenzenes (19). These compounds are subsequently used as starting products for crop protection agents, dyestuffs and rubber chemicals (19). Chlorobenzene is also used as a solvent in degreasing processes (e.g., in metal cleaning operations) and in the dry cleaning industry. It serves as a solvent for paints, adhesives, waxes and polishes and has also been used as a heat transfer medium (6, 63, 92) and in the manufacture of resins, dyes, perfumes and pesticides (92).

Although the annual production rates for chlorobenzene in the United States [140,000 tons in 1975; 130,000 tons in 1981 and 116,000 tons in 1984 (6, 32, 36, 49)], show a decreasing trend, it has been estimated that the consumption of chlorobenzene would grow at an average annual rate of 1-2% in the United States (37). Large manufacturers of chlorobenzene in the United States are Monsanto Co., PPG Industries, and Standard Chlorine Chemical Co. (19). In the late 1970s, approximately 500 tons of chlorobenzene was imported into the United States (32).

In 1989, a total of 60,000 to 70,000 tons of chlorobenzene was produced in the Federal Republic of Germany by two different manufacturers, Bayer AG and Hoechst AG (19). In 1985, the total production in Western Europe was estimated to be 82,000 tons (19). In Eastern Europe, the total production of chlorobenzene in 1988 was calculated

to be 200,000–250,000 tons (19). The production volume in Japan was 28,300 tons in 1988 (19).

According to the Products Register at the National Chemicals Inspectorate [U. Rick, personal communication], monochlorobenzene occurred in ten different chemical products in Sweden in 1990. The estimated annual use of the compound that year in Sweden was 11 to 64 tons. There is no production of chlorobenzene in Sweden.

3.2 Occupational Exposure and Ambient Air Levels

The amount of data available with regard to the potential exposure to chlorobenzene in various types of occupational settings is limited. In Sweden, for example, the National Board of Occupational Health and Safety (an authority responsible for protecting workers who handle chemicals in the workplace from ill-health and accidents) had no information available on the present exposure levels of monochlorobenzene at Swedish workplaces.

A monitoring program of air levels in chlorobenzene- and nitrochlorobenzene-producing plants in the United States, which was performed 1978/79, showed that the chlorobenzene concentrations varied from not detectable to 18.7 mg/m³ (19). Similar concentrations of chlorobenzene have been reported in various field investigations conducted by NIOSH at different types of workplaces in the United States (69c-g). In a Japanese study on the urinary levels of chlorobenzene-associated metabolites in workers at two different plants handling the compound (96), the chlorobenzene levels varied between 7.8–26.7 mg/m³, with a geometric mean of 14.5 mg/m³ (3.15 ppm). A similar study from Belgium (56) showed variations in chlorobenzene concentrations ranging from 0.2–488 mg/m³, the median value being 5.5 mg/m³ (1.2 ppm).

There are no natural sources for chlorobenzene and most releases result from its use as a solvent (6). The substance is delivered into the environment mainly with exhaust air and waste water from production plants, processing industries and from its use as a solvent. In the atmosphere, chlorobenzene is anticipated to degrade slowly by free radical oxidation. Due to its high volatility, chlorobenzene is expected to evaporate rapidly into air when released to surface water, but when released to the ground it has been assumed to first bind to the soil and then migrate slowly to the ground water (6). In January 1987, there was an accidental release of approximately 450 tons of monochlorobenzene to the Baltic Sea outside Kotka, Finland (39). Because the sea was calm and covered with ice, it was believed that most of the chlorobenzene sank to the bottom of the sea. The environmental consequences of this release are not known.

Chlorobenzene is resistant to biodegradation as well as to chemical and physical degeneration (6, 32). In accordance with its relatively high lipid solubility, it has been shown to bioaccumulate in, for example, fish and algae (6). In 1978 it was estimated that almost a total of 80,000 tons of chlorobenzene were released to the atmosphere each year in the United States (32). Apart from an occupational exposure, humans may be exposed to chlorobenzene from drinking water, food, ambient air and consumers' products.

Based on various national surveys, the U.S. EPA has estimated the concentrations of chlorobenzene to be less than 1-5 $\mu\text{g/l}$ in groundwater, and less than 1 $\mu\text{g/l}$ in surface water (32). The magnitude of the potential dietary intake of chlorobenzene was not estimated since the available data were considered insufficient (32). The median concentration of chlorobenzene in ambient air of urban and suburban areas has been calculated at 1.5 $\mu\text{g/m}^3$ (32). Various measurements performed in Germany and The Netherlands showed that the average outdoor air levels of chlorobenzene varied between 0.3 and 1.5 $\mu\text{g/m}^3$ (19).

Like other volatile halogenated hydrocarbons, chlorobenzene may very well be present in the indoor air of, for example, household settings in amounts exceeding those of the ambient air. When the indoor air concentrations of chlorobenzene were measured in the Bavarian city, Hof, Germany, these were found to vary between 0.1 and 4 $\mu\text{g/m}^3$, with a geometric mean of 0.5 $\mu\text{g/m}^3$ (19). Somewhat higher indoor air concentrations were found in various cities in the USA, ranging between not detectable and 72.2 $\mu\text{g/m}^3$, with an average of 16.5 $\mu\text{g/m}^3$ (19).

Chlorobenzene may be formed during the biotransformation of other compounds. It has, for example, been shown that chlorobenzene is a major metabolite of hexachlorocyclohexane, better known as the insecticide Lindane, at least when Lindane is incubated with rat liver microsomes under anaerobic conditions (14).

To summarize, although chlorobenzene may be present in ambient air, the levels are generally considerably lower than those that can be found in industries manufacturing or processing chlorobenzene.

3.3 Analytical Methods for Air Monitoring

NIOSH manual of analytical methods (69) describes a standardized method for sampling and analysis for chlorobenzene in ambient air. The method was revised in 1987 (69b). First a known volume of air is drawn through a charcoal tube to trap the organic vapors present. Then the charcoal in the tube is transferred to a stoppered sample container where the amount of chlorobenzene adsorbed to the charcoal is eluted with carbon disulfide. An aliquot of the desorbed sample is then injected into a gas chromatograph with a flame ionization detector (GC-FID). The amount of chlorobenzene present in the sample is determined by measuring and comparing the areas under the resulting peaks from the sample and those obtained from the injection of standards.

Sampling can be done either actively with adsorption tubes or passively through personal air sampling using passive diffusion techniques. It seems as if most investigators have preferred personal air sampling using a passive organic solvent sampler in the breathing zone, when they measured the occupational exposure to chlorobenzene (56, 71, 96). Using personal air sampling and GC analysis, the detection limit has been reported to be 0.05 ppm (0.23 mg/m^3) for an exposure time of 8 hr in an industrial setting (56). Alternatives to the GC-FID technique have also been used for the analysis of ambient air levels of chlorobenzene; for example, high pressure liquid chromatography (96). To confirm the identity of the compound, GC can be combined with mass spectrometry (71).

A similar technique is used when the amount of chlorobenzene is determined in water samples. The procedure used is the so-called purge-and-trap gas chromatographic procedure, a standard method for the determination of volatile organohalides in drinking water (6). An inert gas is bubbled through the sample so that chlorobenzene is trapped on an adsorbent material. The adsorbent is then heated to drive chlorobenzene onto a GC column.

3.4 Present Occupational Standards

In 1989, ACGIH adopted a TLV-TWA of 10 ppm (46 mg/m³) for the occupational exposure to chlorobenzene in the United States (2). Their previous limit of 75 ppm (345 mg/m³) was considered low enough to prevent narcotic effects or chronic poisoning (92). The suggested reduction from 75 to 10 ppm was done to prevent chlorobenzene-induced injuries to the liver and kidneys. The current OSHA permissible exposure limit is 75 ppm (71b).

The maximum concentration value (the so-called MAK value) of chlorobenzene allowed in occupational settings in the Federal Republic of Germany was established as 50 ppm (230 mg/m³) in 1971 (26); a concentration that still seemed valid in 1990 (56). At present, there are no standards or recommendations for occupational exposure to monochlorobenzene in Sweden (88).

Maximum recommended concentrations in workplace air in the USSR and Czechoslovakia have been reported to be 10 and 43 ppm, respectively (92).