SCOEL/REC/188
Hexachlorobenzene

Recommendation from the
Scientific Committee on Occupational Exposure Limits

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Adopted 9th of March 2016

EUROPEAN COMMISSION

Directorate-General for Employment, Social Affairs and Inclusion
Directorate B —Employment
Unit B.3 — Health and safety

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8-hour TWA:	Not recommended
STEL:	Not relevant
BLV:	150 µg/l as serum or plasma hexachlorobenzene (sampling time is not critical)
Additional categorisation:	Carcinogen group D (non-genotoxic carcinogens and non-DNA reactive carcinogens)
Notation:	Skin

The present Recommendation was adopted by SCOEL on 2016-03-09.

This evaluation is mainly based on ATSDR (2002), Euro Chlor (2005), Greim (2001 and 2002), HCN (2011), IARC (2001), IPCS (1997), NTP (2011),the references cited in these reviews and a literature update (time period 2002–2015).

RECOMMENDATION EXECUTIVE SUMMARY

The critical toxic effects of hexachlorobenzene in humans are hepatic porphyria and liver toxicity. The lowest reported oral dose causing liver toxicity in humans was estimated from an epidemic in Turkey with reported hexachlorobenzene levels of 0.8-3.3 mg/kg bw/day (HCN 2011). No NOAEL was established. At higher doses, also effects on the thyroid, skin, musculo-skeletal system, kidney, immune system and nervous system were reported, which may at least in part be secondary to hepatic porphyria. Hexachlorobenzene is a highly cumulative substance with a long elimination half-life. Due to its cumulative nature, the correlation between hexachlorobenzene levels in air and blood has been poor in industrial hygienic studies. Therefore, biomonitoring is the recommended method to follow-up the occupational exposure to hexachlorobenzene.

There are some studies available on the association between serum/plasma hexachlorobenzene levels and adverse effects in humans. No effects or only minor effects with unclear clinical significance have been seen in these studies at mean serum/plasma hexachlorobenzene levels of ~30–300 µg/l. Sala *et al* (2001) saw a decrease in blood total T4 levels in a subgroup of factory workers with the highest hexachlorobenzene levels in serum (mean serum levels in males were 89.3 µg/l, and in females 18.8 µg/l) and a positive association between γ-GT and hexachlorobenzene levels. No effects on TSH and free T4 levels were, however, seen. In other studies on a Spanish Flix population, no health effects were seen at mean blood hexachlorobenzene levels of ~100 µg/l (Herrero *et al* 1999, Sala *et a*l 1999). Health surveillance data from hexachlorobenzene production suggested increased liver enzyme levels (γ-GT) in a subgroup of workers with plasma hexachlorobenzene levels > 150 µg/l (Drexler and Greim 2005). In an older study by Currier *et al* (1980), no effects were seen even at serum/plasma levels of ~300 µg/l of hexachlorobenzene.

In animals, an oral NOAEL of 0.01 mg/kg bw/day was demonstrated in a 13-week study in monkeys, with effects on the reproductive system and liver occurring at 0.1 mg/kg bw/day. In a 2-generation study, hepatotoxicity and developmental effects were observed in rats at 0.8 and 2 mg/kg bw/day, respectively. Immunological effects in dogs were reported at 0.1 mg/kg bw/day after 1 year. Hexachlorobenzene caused reversible hearing threshold changes and a decrease in plasma T4 levels after 4 weeks of oral dosing at 4 mg/kg bw/day in rats. The NOAEL was 0.16 mg/kg bw/day. Studies in rats and mice showed teratogenic effects at doses of 100 and 40 mg/kg bw, respectively.

Genotoxicity and carcinogenicity

Hexachlorobenzene is carcinogenic in animals causing liver tumours. In humans, some studies have suggested an increased risk for carcinogenicity in humans, whereas the majority have not. Hexachlorobenzene has been mostly negative in bacterial and mammalian genotoxicity tests *in vitro* and *in vivo* at non-toxic doses (ATSDR 2002, Greim 2001, HCN 2011). Induction of liver tumours in animals is considered to be related to general liver toxicity of hexachlorobenzene. Therefore, preventing liver toxicity is likely to prevent the formation of cancer. Hexachlorobenzene is categorised as a SCOEL carcinogen group D (non-genotoxic carcinogens and/or non-DNA reactive carcinogens, for which a true ("perfect") threshold is associated with a clearly founded NOAEL (Bolt and Huici-Montagud 2008).

Overall assessment

Because of the low vapour pressure, potential for significant dermal absorption, and the highly cumulative nature of hexachlorobenzene, the correlation between air and plasma levels is poor. Therefore, biomonitoring is the recommended method to measure cumulative exposure.

Based on the weight of evidence from human studies in occupationally and environmentally exposed people it can be concluded that clinical effects are unlikely at

plasma or serum hexachlorobenzene levels below 150 µg/l. Therefore, *a biological limit value (BLV) of 150 µg/l in plasma or serum is proposed for hexachlorobenzene.* A hexachlorobenzene level of 150 µg/l plasma corresponds approximately to 4 µg/g plasma lipid. Variations in lipid content in plasma/serum may cause some variation in this relation (Phillips *et al* 1989), however, this variability is considered to be of minor importance. Because of the long half-time of hexachlorobenzene, the sampling time is not critical.

Regarding an air limit value, DECOS has previously derived a health-based OEL of 0.006 mg/m^3 based on a NOAEL of 0.01 mg/kg observed in an oral monkey study and applying uncertainty factors for study duration and intra-/interspecies variation. Using a one-compartment model, a BLV of 150 µg/l can be regarded being equivalent for the purpose of comparison to an air level of 0.003 mg/m^3 in occupational exposure. Both of these approaches to derive an air limit for hexachlorobenzene include, however, some uncertainties. In addition, measurement of hexachlorobenzene in air may result in a severe underestimate of the total exposure because of the low vapour pressure, potential for significant skin absorption and cumulative nature of hexachlorobenzene exposure. Therefore, air measurement is not a recommended method to monitor hexachlorobenzene exposure at the workplace and no OEL is recommended.

Other assignments

Sensitisation:
There were no data on sensitisation in humans and no animal experiments according to current guidelines. According to a study from the 1930s, hexachlorobenzene is not a skin sensitiser in guinea pigs (Greim 2001). No sensitiser notation is recommended.

Skin:
The skin absorption rate in rats of neat hexachlorobenzene according to Koizumi *et al* (1991) was 0.9 µg/cm^2/hour. Applying the ECETOC criteria, i.e. exposure of 2000 cm^2 skin to neat substance for one hour (ECETOC 1993), the resulting daily systemic exposure would be 1800 µg (0.9 µg/cm^2/hour x 2000 cm^2 x 1 hour). The recommended BLV is 150 ug/l serum or plasma, which roughly corresponds to inhalation exposure to 33 µg per workday (see Section 7.3.1). This suggests that skin absorption may contribute greatly (well over 10% of the total body burden, ECETOC, 1993) to the body burden. As a relatively high dermal absorption is expected compared with the systemic NOAEL, a skin notation is recommended.

Hearing:
In rats, hexachlorobenzene have caused hearing threshold changes after 4 weeks oral dosing at 4–16 mg/kg bw/day. No data on combined effects with noise are available. No noise notation is suggested.

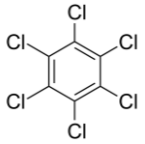
Sampling, measurement and analysis

No measurement difficulties are foreseen at the suggested BLV level.

RECOMMENDATION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR HEXACHLOROBENZENE

RECOMMENDATION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

Name:	Hexachlorobenzene
Synonyms:	HCB, perchlorobenzene, pentachlorophenyl chloride
Molecular formula:	C6Cl6
Structural formula:	
EC No.:	204-273-9
CAS No.:	118-74-1
Molecular weight:	284.78 g/mol
Boiling point:	323–326 °C (sublimes)
Melting point:	227–231.8 °C
Vapour pressure (20 °C):	1.1–2.3 × 10-3 kPa
Conversion factors:	1 ppm = 11.8 mg/m^3
(20 °C, 101.3kPa)	1 mg/m^3 = 0.08 ppm

Hexachlorobenzene is a fully chlorinated industrial aromatic hydrocarbon. At ambient temperature it is a white needle-like crystalline solid and stable under normal temperatures and pressures. It is practically insoluble in water but is very soluble in fat and oils. In organic solvents, it is slightly soluble in ethanol, sparingly soluble in carbon tetrachloride, soluble in diethyl ether, chloroform, carbon disulphide and very soluble in benzene (ATSDR 2002, IARC 2001, NTP 2011).

Hexachlorobenzene has a high octanol/water partition coefficient (log K_{ow}) and a low vapour pressure (ATSDR 2002, Euro Chlor 2005, Greim 2001, IARC 2001). An odour threshold for hexachlorobenzene is not available (ATSDR 2002). When hexachlorobenzene decomposes it emits highly toxic fumes of chlorides (ATSDR 2002, NTP 2011).

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for hexachlobenzene is provided by ECHA, as summarised in Tables 1 and 2.

Table 1: Hexachlorobenzene: Classification according to part 3 of Annex VI, table 3.1 (list of harmonised classification and labelling of hazardous substances of Regulation (EC) No1272/2008 (ECHA 2015).

Index no.	Internat. Chemical Identification	EC no.	CAS no.	Classification		Labelling		
				Hazard Class & Category Code (s)	Hazard statement code (s)	Pictogram Signal Word Code (s)	Hazard statement code (s)	Suppl. Hazard statement code
602-065-00-6	hexachlorobenzene	204-273-9	118-74-1	Carc. 1B STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H372 ** H400 H410	GHS09 GHS08 Dgr	H350 H372 ** H410	

Table 2: Hexachlorobenzene: Classification according to part 3 of Annex VI, table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC of Regulation (EC) No1272/2008 (ECHA 2015).

Classification	Risk Phrases	Safety Phrases	Indication of danger	Concentration Limits	
				Concentration	Classification
Carc. Cat. 2; R45 T; R48/25 N; R50-53	45 48/25 50/53	53 45 60 61	T N		

3. CHEMICAL AGENT AND SCOPE OF LEGISLATION

Hexachlorobenzene is a hazardous chemical agent in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Hexachlorobenzene is also a carcinogen or mutagen for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and falls within the scope of this legislation.

4. EXISTING OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for hexachlorobenzene exist in a number of countries, as shown in the table below. The values presented below represent examples and are not an exhaustive listing of all limit values within the EU and other countries.

Table 3: Existing OELs for Hexachlorobenzene; adapted from the GESTIS database (GESTIS 2015).

4.1. EU-countries	TWA (8 hrs)	STEL (15 min)	
	mg/m³	mg/m³	**References**
Belgium	0.002		RD (2014)
Denmark	0.025		BEK (2011)
EU	"not recommended/not relevant"		SCOEL (2013)
Finland	0.0002		MoSH (2012)
France	0.9		INRS (2012)
Ireland	0.03		HSA (2011)
Latvia	0.9		GESTIS (2015)
Poland	0.5		MLSP (2002)
Spain	0.002		INSHT(2011)
The Netherlands	0.025		SER (2007)
4.2. Non EU-countries	mg/m³	mg/m³	
Canada (Ontario)	0.002		Ontario Ministry of Labour (2013)
Canada (Québec)	0.025	0.05	IRSST (2010)
Singapore	0.025		GESTIS (2015)

In addition to the above OELs, there are also biological threshold limit values established in the following country:

- Germany: A BAT value of 150 µg/l measured as mg of hexachlorobenzene per liter of plasma/serum, measured (sampling time is not fixed) was established (DFG 2015) (the BAT value "Biologischer Arbeitsstoff-Toleranz-Wert": biological tolerance value for occupational exposures is defined as the maximum permissible quantity of a chemical substance or its metabolites or the maximum permissible deviation from the norm of biological parameters induced by these substances in exposed humans).

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence and use

Hexachlorobenzene (HCB) does not occur naturally (ATSDR 2002 and 2015, HCN 2011 IARC 2001, NTP 2011). It is a synthetized chlorinated hydrocarbon industrial chemical, which was first introduced in 1940's and has been used mainly as a fungicide (Euro Chlor 2005).

HCB is one of the most persistent environmental pollutants due to its chemical stability and resistance to biodegradation. Since the 1960's, HCB has been progressively banned in many individual countries and at global scale under the Stockholm Convention (adopted in 2001) on persistent organic pollutants (POPs), which entered into force in May 2004.

Although HCB is no longer used today, it is still ubiquitous in the environment, including rural and remote locations (ATSDR 2015). This is mainly a consequence of its past use and because it is persistent and bio-accumulative. Still today it contaminates the food chain, indeed it is detected in breast milk of humans and in the blood of the general population. Systematic data collection and analyses of the current levels have been carried out by ATSDR (2002 and 2015), HCN (2011), IARC (2001), and NTP (2011). Overall, a declining temporal trend in the contamination of the environment, food chain, human bio-fluids and tissues is being progressively documented, eventually as a result of the implementation of the ban at national and international levels (Angerer et al 2003, Bjerregaard et al 2013, Fång et al 2015, Fernández-Rodríguez et al 2015, Hardell et al 2010, Martí-Cid et al 2008, Specht et al 2015).

5.2. Production and use information

Although hexachlorobenzene is not currently manufactured as a commercial end product, according to (ATSDR 2015, Bailey 2001, Euro Chlor 2005, HCN 2011, IARC 2001) it is still formed as a by-product during the manufacture of other chlorine containing compounds, such as:

- chlorinated solvents (*e.g.*, tetrachloroethylene, trichloroethylene, carbon tetrachloride),
- other chlorinated compounds (*e.g.*, vinyl chloride, trichlorobenzenes, trichlorotoluenes, chlorophenols),
- pesticides (e.g., tetrachloroisophthalonitrile (chlorothalonil), pentachloronitrobenzene (PCNB), 4-amino-3,5,6-trichloropicolinic acid (picloram), pentachlorophenol (pentachlorophenol), dimethyltetrachloroterephthalate (DCPA, atrazine, propazine, simazine, and mirex).

In addition, HCB may be formed from impurities in a wide range of industrial processes:

- combustion of municipal waste or in waste streams from chlor-alkali plants (ATSDR 2015, Eicman et al 1981, IARC 1979, Oberg and Bergstrom 1985, Oehme et al 1987, Tiernan et al 1990),
- hazardous waste incineration (Bailey 2001, Cohen et al 1995, Oberg and Bergstrom 1985,),
- medical waste incineration (Bailey 2001),
- metals industry (Bailey 2001, Cohen et al 1995),
- iron ore sintering (Bailey 2001, Cohen et al 1995),
- coal combustion (Bailey 2001),
- cement production (Bailey 2001),
- wood-preserving plants (ATSDR 2015, Leger 1992).

Bailey (2001) estimated the total amount of hexachlorobenzene released as a by-product in the production of all chlorinated solvents to be 0.3 kg/year in the mid-1990s. At that time, the hexachlorobenzene release through the use of eight major pesticides containing hexachlorobenzene accounted for 1270 kg/year (Bailey 2001).

Current estimates of hexachlorobenzene as a by-product or impurity were not available. In China hexachlorobenzene is still being produced (Wang et al 2010). China has been listed as an exemption from the Stockholm Convention for production and use of hexachlorobenzene as an intermediate. Both, China and Russia still produce pentachlorophenol (PCP) from hexachlorobenzene by caustic soda hydrolysis. Currently, this is believed to be the only use of hexachlorobenzene as chemical intermediate (Euro Chlor 2005). In 2009, HCB was available from 19 suppliers worldwide including 14 US suppliers (ChemSources 2010, NTP 2011).

Regarding the use of HCB it is believed that none of the historical applications listed below to be currently practiced in North America or Western Europe (Bailey 2001):

- fungicide;
- military pyrotechnic smokes;
- carbon anode treatment;
- aluminum fluxing and degassing;
- synthetic rubber peptizing agent;
- wood preservation (HCB as active material);
- intermediate in organic syntheses.

In recent years, stocks of organochlorine pesticides, including hexachlorobenzene, have been collected from developing countries to be incinerated in the EU.

5.3. Occupational exposure

Although all uses of hexachlorobenzene as a pesticide have been banned, occupational exposure is possible in industries where hexachlorobenzene is produced for on-site use and processing, and occurs in considerable amounts as an incidental by-product or contaminant in chlorinated solvents, other chlorinated compounds and pesticides. Possibly exposed workers are furthermore military or fire-fighting personnel who use pyrotechnic mixtures releasing hexachlorobenzene, and those involved in the handling and treatment of wastes (ATSDR 2002).

According to the Health Council of the Netherlands (HCN 2011), the potential exposure to hexachlorobenzene of current workers in the Netherlands cannot be estimated, as no quantitative information on the production of chemicals in which hexachlorobenzene is potentially formed as an impurity is available.

There are no recent data on occupational exposure to hexachlorobenzene. Available data show a poor association between blood and airborne hexachlorobenzene concentrations

(ATSDR 2002, Euro Chlor 2005, Greim 2001, IARC 2001, IPCS 1997). This finding is a result of the low vapour pressure, good skin absorption and highly cumulative effect of hexachlorobenzene. Currier et al (1980) reported air concentrations of hexachlorobenzene in the chlorinated solvent production of < 1–13 ppb; wipe samples from work areas ranged from 0.03 to 124 µg/100 m^2. Hexachlorobenzene concentrations in the serum or blood of a group of workers (n was 50 in 1974 but decreased to 44 in 1977) were 311 and 312 µg/l serum in 1974 and 1975, respectively, and 160 and 170 µg/l blood in 1976 and 1977, respectively. Blood levels of hexachlorobenzene were strongly correlated with the number of working years in this plant, but not with hexachlorobenzene concentrations in air or wipe samples (Currier et al 1980).

Workers who were exposed until 1980 to hexachlorobenzene at concentrations of 2.1-10.8 mg/m^3 (0.18–0.91 ppm) showed serum values of 534 µg/l. After this, exposure levels were decreased in the plant to 0.012–0.022 mg hexachlorobenzene/m^3 (0.001-0.002 ppm). However, when the blood levels of these same workers were investigated later (between 1983 and 1990), they still had serum hexachlorobenzene levels of more than 500 µg/l. For example, in 1989 (9 years after the air levels had been reduced), the mean serum concentration of these workers was 575 µg/l (Richter et al 1994, cited in Greim 2001).

5.4. Routes of exposure and uptake

HCB is no longer produced (as an end-product) or used as a pesticide. Consequently, the current potential for exposure of the general population appears to be very limited. However, some exposure is possible, as many studies have detected small amounts in food and air samples, particularly in those with high lipid content such as meat, poultry, and fish. Traces of HCB have been found in almost all people tested for HCB or its metabolites. These amounts of HCB are most likely the result of consumption of low levels in food and contaminated drinking water (ATSDR 2002). Other sources of exposure may include contact with contaminated soil and air, but general population exposure to HCB via inhalation or dermal contact would be much less compared to potential oral exposure (NTP 2011).

In occupational settings, in addition to possible inhalation exposure, skin exposure and uptake via the skin may significantly contribute to the total exposure to HCB.

6. MONITORING EXPOSURE

Determination of HCB in the air and in biological materials generally consist of extraction of the sample into organic solvents, often followed by a clean-up step to remove interfering compounds and analysis by gas chromatography (GC) coupled with electron capture detection (ECD) or mass spectrometry (MS) (ATSDR 2015).

Although SCOEL does not recommend OEL values for HCB, the implementation of which would need air analysis, we refer at this stage to ATSDR (2002 and 2015), and IARC (2001), which summarized several analytical methods that may have been be approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH) or Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA).

Regarding the implementation of the BLV, as recommended by SCOEL, HCB can be monitored in blood or plasma by applying the following methods:

- MAK 1989: Lewalter and Ellrich (1991), Organochlorine compounds in whole blood and plasma;
- MAK 2001: Hoppe and Weiss (2003), Chlorinated aromatic hydrocarbons.

Table 4: Overview of sampling and analytical methods for biomonitoring HCB in the workplace.

Method	Analysis	Standard deviation (rel)(*Sw*)*	Prognostic range	Recovery (%)	Detection limit	References
MAK 1989: Organochlorine compounds in whole blood and plasma	GC- MS	5.3% - 2.7%	11.8 - 6.7%	88% at a concentration of 0.5 µg /l	0.02 µg/l HCB in blood	Lewalter and Ellrich (1991)
MAK 2001: Chlorinated aromatic hydrocarbons	GC	8.7% - 3.2%	19.7 - 7.2% At concentrations of 20 and 200 µg HCB per liter blood and where n = 10 determinations	86 - 1.5 %	100 µg/l HCB in blood	Hoppe and Weiss (2003)

* Within-series imprecision

7. HEALTH EFFECTS

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

No data on absorption at inhalation exposure were available.

Dermal absorption in rats was tested by Koizumi (1991) under occlusive conditions. Hexachlorobenzene was dissolved in tetrachloroethylene. Within 6 hours 1 %, and within 24 hours 2.7 %, of the dermally applied hexachlorobenzene was absorbed. The absorbed fraction increased up to 9.7 % 72 hours after the application. An absorption rate of 0.9 µg/cm^2/hour was calculated (Koizumi 1991).

Human oral absorption is up to 85 % and decreases at higher blood concentrations of hexachlorobenzene (Euro Chlor 2005, HCN 2011). The solvent affects the oral absorption of HCB: gastrointestinal absorption of HCB in animals has been shown to vary from 6% when administered in water to 82% when administered in vegetable oils.

Orally absorbed hexachlorobenzene distributes widely in all tissues and mother milk and accumulates in fat. Hexachlorobenzene is highly lipophilic and serum lipid levels have an effect on background serum hexachlorobenzene levels (Phillips et al 1989). Hexachlorobenzene readily crosses the placenta and accumulates in foetal tissue in several animal species. In mammals, hexachlorobenzene metabolism is slow via CYP450, with further conjugation with glutathione. The main metabolites are pentachlorophenol, pentachlorobenzene and tetrachlorobenzene, with lesser amounts of tetrachlorohydroquinone, 2,4,5-trichlorophenol and 2,3,4,6- and 2,3,5,6-tetra-chlorophenols. Also small amounts of lower-chlorinated benzenes and phenols as well as S-conjugated phenols and benzenes have been detected in other studies (Greim 2001, HCN 2011). Humans and animals excrete hexachlorobenzene mainly unchanged in faeces after oral or inhalatory absorption with some part being excreted in urine as its

metabolites (HCN 2011). The elimination half-life of hexachlorobenzene in humans is long, reported half-lives ranging from 2 to 6 years (Greim 2001, To-Figueras et al 2000). In monkeys, a half-life of 3 years has been reported and in rats, reported half-lives are up to 5 months (Greim 2001).

7.1.1. Biological monitoring

With detection limits in the low ppb (ng/g) range and a good sensitivity, whole blood, serum or plasma are often used to assess human (both environmental and occupational) exposure to hexachlorobenzene (Angerer et al 1991 and 2003, ATSDR 2002, IARC 2001). Methods for adipose tissue, breast milk, urine and semen have been reported (ATSDR 2002, IARC 2001). They are, however, not suitable or not sufficiently sensitive for occupational monitoring exposure (ATSDR 2002). Indirect biomarkers [γ-glutamyl transferase (γ-GT) in blood, uroporphyrin and δ-aminolevulinic acid in urine, and coproporphyrin in faeces] are not specific for hexachlorobenzene and are therefore also of limited usefulness in monitoring of exposed workers (HCN 2011).

Euro Chlor (2005) summarised the mean levels of hexachlorobenzene in blood and serum of the general human population in various countries. Age has a strong influence on the blood hexachlorobenzene levels. In European countries, the values were generally less than 1 µg/l with concentrations up to 4 µg/l in Germany and Iceland. However, in Portugal and Spain elevated values with a maximum of 124 µg/l were reported.

In 1999, German reference values for adults in whole blood ranged from 0.4 to 4.0 µg/l (Angerer et al 2003). In 2003, reference values were 0.12–1.19 µg/l depending on age (UBA 2003), the mean concentration being 0.44 µg/l and the 95th percentile for the adult, working age (age 19–69 years) population being 2.5 µg/l (range 0.3–4.8 µg/l (Becker et al 2002, UBA 2003). Blood collected in 2000–2002 from 226 pregnant women (aged 19–41 years) living in an industrialised area of Germany showed hexachlorobenzene concentrations of 0.036–0.53 µg/l (mean 0.15 µg/l) (Wittsiepe et al 2008). Schettgen et al (2011) reported levels of 0.18–0.742 µg/l plasma in adults of the general population in southern Germany.

Owing to its persistence and lipophilicity, mean hexa¬chlorobenzene levels in human fatty tissue in various countries range from tens to hundreds of ng/g (w/w) (Euro Chlor 2005). Hexachlorobenzene may also be detected in human breast milk (ATSDR 2002, Euro Chlor 2005, NTP 2011) and hair (Covaci et al 2008, Tsatsakis et al 2008).

In occupationally exposed people, serum levels up to > 500 µg/l have been measured in the past (see Section 2.2.2). Due to its cumulative nature, no correlation between air levels and blood hexachlorobenzene levels has been established.

7.2. Acute toxicity

7.2.1. Human data

No data were reported on acute toxicity of hexachlorobenzene in humans (ATSDR 2002, Greim 2001, HCN 2011).

7.2.2. Animal data

In animals, hexachlorobenzene has a low acute toxicity. Oral LD50 values range from 1 700 mg/kg bw in cats up to 3 500–10 000 mg/kg bw in rats. The inhalation LC50 is 1 600 mg/m^3 in cats, 1 800 mg/m^3 in rabbits, up to 3 600 mg/m^3 in rats and 4 000 mg/m^3

in mice. Clinical symptoms were convulsions, tremors, weakness, ataxia and paralysis (ATSDR 2002, Euro Chlor 2005, Greim 2001, HCN 2011, Lehnert and Greim 1995).

7.3. Specific Target Organ Toxicity/Repeated Exposure

The main effect of long-term hexachlorobenzene exposure is a reduction of uroporphyrinogen decarboxylase activity, an enzyme of haem biosynthesis, resulting in accumulation of uroporphyrinogen intermediates in the liver and the clinical outcome of porphyria cutanea tarda with specific skin lesions and liver effects (liver enlargement, hepatitis). Human data have also shown neurotoxicity as well as effects on the thyroid, musculo-skeletal system, kidney and immune system (HCN 2011, ATSDR 2002).

7.3.1. Human data

In Turkey, several studies investigated populations having consumed bread made from hexachlorobenzene contaminated flour between 1955 and 1959 (500 people fatally poisoned, 4 000 becoming sick). The ingested dose of hexachlorobenzene was estimated to be 0.05–0.2 g/day corresponding to 0.8–3.3 mg/kg bw/day in a 60-kg adult (Cam and Nigogosyan 1963). Hepatomegaly, muscle weakness, paraesthesia, neuritis and myotonia, skin lesions and reproductive toxicity were reported. This is the lowest reported oral dose with observed hepatotoxic effects in humans (HCN 2011). A no observed adverse effect level (NOAEL) could not be derived.

Herrero et al (1999) reported relatively high serum levels of hexachlorobenzene (mean hexachlorobenzene in factory workers: 93.4±223.3 µg/l; non-factory workers: 16.9±17.1 µg/l) in residents of Flix, Spain, a population living near an organochlorine compound producing factory. Investigated residents (253 males and 351 females, 185 had been employed in the plant, 14–91 years old) had an average porphyrin concentration in urine of 98±69 nmol/l (range 9–1 009 nmol/l). No correlation between hexachlorobenzene in serum and porphyrin excretion was detected. Neither did porphyrin levels correlate with occupation in the factory (Herrero et al 1999). In a further analysis of individual urinary porphyrins within 241 Flix residents with a median serum hexachlorobenzene level of 21.7 µg/l, no hexachlorobenzene related increase in porphyrin levels was seen (Sunyer et al 2002). A cross-sectional study of the same Flix population showed no significant increase in the risk for adverse health effects, chronic diseases, porphyria cutanea tarda, thyroid diseases, Parkinson's disease or impaired reproduction. The median hexachlorobenzene concentration in serum was 36.7 µg/l with a 95th percentile of 110 µg/l (Sala et al 1999).

The same population was further investigated for thyroid and liver effects (Sala et al 2001). A significant negative association was seen between serum hexachlorobenzene levels and total thyroxine (T4) [but not free T4 or thyroid stimulating hormone (TSH)] and a positive association was seen with the liver enzyme γ-GT although both T4 and γ-GT levels were in the normal range in 92 % of the subjects. When a subgroup of 75 male and 11 female factory workers with higher hexachlorobenzene concentrations in serum (mean serum hexachlorobenzene in males 89.3 µg/l, in females 18.8 µg/l) were compared to never workers (mean in males 14.1 and in females 17.5 µg/l) significantly lower T4 levels were observed in the factory workers. In males, all abnormal T4 and γ-GT levels (below or above reference limits, respectively) were in factory workers. Adjustment of the results for alcohol consumption, sex, age, body mass index (BMI), recent weight loss and smoking did not affect the results (Sala et al 2001).

Currier et al (1980) reported health surveillance data from 50 workers from the production of chlorinated solvents with mean plasma or blood hexachlorobenzene levels ranging from about 311–312 ppb in plasma in 1974–1975 (corresponding to ~319-320 µg/l) to 160–170 ppb in blood in 1976–1977 (corresponding to ~170-180 µg/l). Compared to the control group, no statistically significant differences

were observed in biochemical parameters and liver enzymes (uroporphyrin and coproporphyrin in urine, lactate dehydrogenase, alkaline phosphatase, total bilirubin, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-GT, haemo¬globin and haematocrit).

In the BAT (biological tolerance value) documentation of the German MAK Commission (Drexler and Greim 2005), health surveillance results were reported from a group of 258 German workers employed until 1993 in the production of hexachlorobenzene. The mean plasma hexachlorobenzene concentration was 30.3 µg/l (1997–2001), with a maximum of 330 µg/l and a median of 15.0 µg/l. In workers with mean hexachlorobenzene concentrations below 150 µg/l plasma, the mean γ-GT concentration was 32.4 U/l, which was in the same range (30.9 U/l) as that for workers with hexachlorobenzene concentrations below 32 µg/l. In 3 workers with hexachlorobenzene concentrations between 150 and 200 µg/l plasma and in 4 workers with hexachlorobenzene concentrations above 200 µg/l plasma, mean γ-GT concentrations of 48.7 U/l and 96.0 U/l, respectively, were determined (Drexler and Greim 2005). The NOAEL in this study for liver enzyme induction was 150 µg/l plasma. This steady-state plasma hexachlorobenzene level of 150 µg/l can be (roughly) converted to a daily dose (D) using the following one-compartment model-based formula: steady-state concentration (Css) = 1.44 × T½ × D/Vd × t, where T½ (half-time) is 6 years (2 190 days), Vd (volume of distribution) is 7 l/kg, and t (dosing interval) is 1 day. Using this formula, SCOEL estimates that a plasma level of 150 µg/l corresponds to a daily dose of 0.33 µg/kg bw/day. This can be further estimated to correspond to an inhaled dose of 3.26 (~3.3) µg/m^3 as an 8-hour TWA at occupational exposure of 5 days/week (assuming a body weight of 70 kg, an inhaled amount of 10 m^3 per day and equal absorption via inhalation and the oral route). A similar one-compartment based model has been used also by Aylward et al (2010) to calculate lipid adjusted biomonitoring equivalents for guidance values given for human environmental exposure (Aylward et al 2010). Aylward's estimated serum lipid-adjusted hexachlorobenzene concentrations for intakes of 1.3–20 ng/kg bw were 16–250 ng/g lipid (corresponding to lipid unadjusted values of ~0.7-11 µg/l). It should be noted that these are for continuous (7 d/week) exposure.

In studies investigating thyroid parameters, an association between body hexachlorobenzene levels (a maximum of 65.8 ng/g lipids) and decreased free and (in some cases) also total T4 levels was seen in Innuits, Mohawks (single serum sample) or pregnant women (repeated serum samples) (Chevrier et al 2008, Dallaire et al 2009, Schell and Gallo 2010). In newborns, on the other hand, an association was seen with increased free T4 levels (Dallaire et al 2008). Other studies did not find a correlation between hexachlorobenzene exposure and thyroid hormone levels (Meeker et al 2007). No conclusions on the causality of the effects or dose-effect relationships can be made based on these studies.

7.3.2. Animal data

7.3.2.1. Inhalation

There were no relevant repeated inhalation toxicity data available on hexachlorobenzene.

7.3.2.2. Oral exposure

In 90-day oral studies conducted in monkeys, effects on the female reproductive system and liver were seen. The effects seen at the lowest dose included marginal microscopical changes in egg cells with unknown relevance. A NOAEL of 0.01 mg/kg bw/day can be derived from these studies (Babineau et al 1991, Bourque et al 1995, Jarrell et al 1993, Sims et al 1991). At 0.1 mg/kg bw/day, degeneration of ovarian follicles occurred and

liver changes (hepatocellular vacuolation and intrahepatic cholestasis) were observed at 1 mg/kg bw/day. Increased excretion of porphyrins was not detected.

Rats dosed for 15 weeks at dose levels of 0, 0.5, 2, 8 and 32 mg/kg bw/day showed liver effects at the two highest doses (Kuiper-Goodman et al 1977). At 2 mg/kg bw/day, induction of xenobiotic metabolising enzymes was seen. Increased porphyrin levels were seen at the lowest dose level in females only.

In a 90-days oral study in specific pathogen free pigs, the oral NOAEL was 0.05 mg/kg bw/day, based on hepatocellular hypertrophy observed at doses of 0.5 mg/kg bw/day and higher (Den Tonkelaar et al 1978).

In a 2-generation study in rats, degenerative changes in the liver occurred at 0.8 mg/kg bw/day, preneoplastic foci at 4 mg/kg bw/day and liver tumours at about 7.5 mg/kg bw/day. The NOAEL in this study was 0.16 mg/kg bw/day (Arnold et al 1985, Arnold and Krewski 1988).

Hexachlorobenzene has exhibited immunosuppressive effects in mice and immunostimulatory effects in rats. The lowest effective dose for immunological effects (increased severity of nodular hyperplasia of the gastric lymphoid tissue) was observed in dogs with a lowest observed adverse effect level (LOAEL) of 0.1 mg/kg bw/day after one year of exposure (HCN 2011).

Effects on hearing were studied in rats dosed orally at the doses of 0, 0.16, 4 and 16 mg/kg bw/day for 4 weeks (Hadjab et al 2004). At the mid-dose (4 mg/kg bw/day), reversible threshold changes were seen at 2–16 kHz frequencies. Permanent changes at all frequencies tested (1–32 kHz) were seen at 16 mg/kg bw/day. No cochlear hair cell loss or alterations in stereocilia were seen. No interactions with noise were studied. At 4 and 16 mg/kg bw/day, a decrease in plasma T4 levels was also seen.

Thyroid effects were seen also in male Syrian hamsters exposed to 10 mg/kg bw/day (LOAEL) in the diet for 28 weeks. These included increased thyroid gland weights (ca. 2.5-fold), decreased serum triiodothyronine (T3) levels, increased sodium iodide uptake (ca. 3-fold), and unchanged serum T4 levels (Greim 2001, HCN 2011).

At higher doses, also effects on bone and muscle have been reported (HCN 2011).

In the Netherlands, the Dutch Expert Committee on Occupational Safety (DECOS) (HCN 2011) has proposed an OEL of 0.006 mg/m^3 based on a subchronic monkey study with a NOAEL of 0.01 mg/kg bw/day. Uncertainty factors applied include 2 for extrapolation from subchronic to chronic exposure, 2 for interspecies extrapolation and 3 for intraspecies variability resulting in a safe oral intake level of 0.83 µg/kg bw/day. This can be converted to an OEL (assuming similar absorption via the inhalatory and oral routes) of 0.006 mg/m^3.

7.3.2.3. Dermal exposure

No relevant data available.

7.3.3. In vitro data

No relevant data available.

7.4. Irritancy and corrosivity

7.4.1. Human data

No data were available.

7.4.2. Animal data

In an inadequately reported study, hexachlorobenzene was slightly irritating to skin but not to eyes (Greim 2001). No information on species is available.

7.4.3. In vitro data

No relevant data available.

7.5. Sensitisation

7.5.1. Human data

No studies on sensitisation caused by hexachlorobenzene in humans were available.

7.5.2. Animal data

In a shortly reported study from the 1930s, hexachlorobenzene was not a skin sensitiser in guinea pigs (Greim 2001).

7.5.3. In vitro data

No relevant data available.

7.6. Genotoxicity

7.6.1. Human data

A micronucleus test with human peripheral lymphocytes of hexachlorobenzene exposed workers was negative (ATSDR 2002, Greim 2001, HCN 2011).

7.6.2. Animal data

Hexachlorobenzene did not induce single-strand breaks or formation of 8-hydroxy-deoxyguanosine in the liver of mice, and the observed increase in replicative DNA-synthesis in mice was not dose-dependent (Greim 2001). In addition, two dominant-lethal tests in rats, and two Comet assays in several organs in rats and mice were negative (ATSDR 2002, Greim 2001, HCN 2011).

7.6.3. In vitro

Hexachlorobenzene was mostly negative in bacterial and mammalian cells (ATSDR 2002, Ennaceur et al 2008, Greim 2001, HCN 2011).

Overall, it can be concluded that hexachlorobenzene is not genotoxic at non-toxic doses (ATSDR 2002, Greim 2001, HCN 2011).

7.7. Carcinogenicity

7.7.1. Human data

There are some studies showing an increased risk for cancer in humans at high hexachlorobenzene serum concentrations (breast cancer: Charlier et al 2003 and 2004 cited in ATSDR 2002, HCN 2011); non-Hodgkin's lymphoma: Spinelli et al 2007; high Epstein-Barr virus antibody titres: Hardell et al 2009). However, on the other hand there are much more studies without any correlation between hexachlorobenzene exposure and cancer (breast cancer: Itoh et al 2009, Iwasaki et al 2008, Lopez-Carrillo et al 2002, Pavuk et al 2003, Raaschou-Nielsen et al 2005; non-Hodgkin's lymphoma: Cantor et al 2003, Cocco et al 2008, Quintana et al 2004; prostate: Hardell et al 2006; testicular germ cells: Biggs et al 2008). Therefore, human data are not sufficient for a clear evidence of human carcinogenicity of hexachlorobenzene.

7.7.2. Animal data

In animals, hexachlorobenzene is carcinogenic (ATSDR 2002, Greim 2001, HCN 2011, NTP 2011). Oral exposure to hexachlorobenzene increases the incidence of tumour formation in the liver in rats, mice and hamsters. In addition, bile duct adenocarcinoma were observed in rats; renal cell carcinoma in rats, mice and hamsters; lymphosarcoma in rats, mice and hamsters; adrenal hyperplasia and pheochromocytoma in rats; parathyroid adenomas in rats and hemangioendothelioma and thyroid tumours in hamsters. Since hexachlorobenzene is not genotoxic, the carcinogenic mechanism of hexachlorobenzene is likely to be thresholded and related to liver toxicity (Greim 2001, HCN 2011, NTP 2011).

7.8. Reproductive toxicity

7.8.1. Human data

7.8.1.1. Fertility

No evidence of adverse effects of hexachlorobenzene on human fertility has been described. There was no difference in people of Xinin, China, in reproductive outcomes before and after cessation of agricultural uses of hexachlorobenzene (Huang et al 1989). Also, no effect was observed on the proportion of male offspring in the Turkish poisoning collective (consumption of bread made of hexachlorobenzene treated grain 1955–1959) with diagnosed porphyria cutanea tarda (Jarrell et al 2000). No further studies investigating the effects of hexachlorobenzene on human fertility were available.

7.8.1.2. Developmental toxicity

In the Turkish poisoning, with adults consuming an estimated amount of 0.8–3.3 mg/kg bw/day of hexachlorobenzene, an association between exposure to hexachlorobenzene and spontaneous abortion, stillbirth and death in early childhood was reported (HCN 2011). However, these effects may be due to general toxicity of high hexachlorobenzene body burdens rather than specific interference with developmental processes (HCN 2011). The Spanish (Flix) study in hexachlorobenzene exposed mothers did not report increased spontaneous abortion, stillbirth and death despite a 5-fold higher average hexachlorobenzene blood level (Sala et al 1999). Other studies suggesting developmental effects in humans (e.g. increased risk of undescended testis, or impaired development of locomotor skills) have very small sizes or very low hexachlorobenzene levels (HCN 2011). This applies also to some more recent studies proposing an association between endocrine disrupting persistent organic pollutants (including hexachlorobenzene) and hypospadias at low environmentally relevant levels (0.2 ng/g lipids or > 0.26 µg/l serum, respectively) (Giordano et al 2010, Rignell-Hydbom et al 2012). There is no support for

these effects from animal studies or from epidemiological studies involving clearly elevated blood hexachlorobenzene levels. Thus, human epidemiological studies are insufficient for an evaluation of developmental toxicity.

7.8.2. Animal data

7.8.2.1 Fertility

No effects on fertility were observed in a 2-generation study in Sprague-Dawley rats up to 2.0 mg/kg bw/day and in two dominant-lethal tests in rats up to 60 mg/kg bw/day or 221 mg/kg bw/day (Arnold et al 1985 and 1986).

In 13-week studies in monkeys, a NOAEL of 0.01 mg/kg bw/day was reported, and at 0.1 mg/kg bw/day, degeneration of follicles in females was observed. Higher doses resulted in more severe follicular degeneration (Babineau et al 1991, Bourque et al 1995, Jarrell et al 1993, Sims et al 1991).

7.8.2.2 Developmental toxicity

The occurrence of cleft palate, renal agenesis, and minor skeletal abnormalities in CD-1 mice at 100 mg/kg bw/day (together with significant increased maternal liver weights) or increased incidences of sternal defects and 14th rib formation at 40 mg/kg bw/day in Wistar rats without maternal toxicity are consistent with a possible teratogenicity of hexachlorobenzene (Courtney et al 1976, Khera 1974). A neurodevelopmental study showed hyperactivity in rat pups with a LOAEL of 2.5 mg/kg bw/day based on minimal neurodevelopmental effects at the lowest tested dose (Goldey and Taylor 1992). The NOAEL for developmental effects in rats was 0.4 mg/kg bw/day, based on reduced pup viability at 2 mg/kg bw in a 2-generation study (Arnold et al 1985 and 1986). Immunodevelopmental effects were seen in rats exposed in utero and during lactation: the antibody response to tetanus toxoid was increased at doses (for the dams) of 0.2 mg/kg bw/day (lowest dose applied) and higher (HCN 2011). In none of these studies were internal serum levels calculated for comparison of effects.

7.8.3. In vitro data

No relevant data available.

7.9. Mode of action and adverse outcome pathway considerations

The most critical effect of hexachlorobenzene in humans and in animals is liver toxicity. Liver is also the target organ for carcinogenic effects. Hexachlorobenzene is not genotoxic. According to the SCOEL view, the carcinogenicity is mediated through a thresholded mechanism related to general liver toxicity. Therefore, preventing liver toxicity will prevent the formation of cancer. Hexachlorobenzene is categorised as a SCOEL carcinogen group D (non-genotoxic carcinogens and/or non-DNA reactive carcinogens, for which a true ("perfect") threshold is associated with a clearly founded NOAEL; Bolt and Huici-Montagud 2008).

7.10. Lack of specific scientific information

There are no such major data gaps which would prevent the setting of a health-based biological limit value (BLV) for hexachlorobenzene.

8. GROUPS AT EXTRA RISK

No specific data on groups at extra risk were identified.

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