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Recommendation from the Scientific Committee on Occupational Exposure Limits for Hexachlorobenzene

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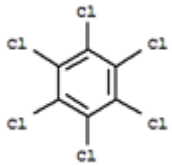
8-hour TWA:	Not recommended
STEL (15-min):	Not relevant
BLV:	150 µg/l serum or plasma
Additional categorisation:	Carcinogen group D (non-genotoxic carcinogens and non-DNA reactive carcinogens)
Notation:	Skin

This evaluation is mainly based on ATSDR (2002), Greim (2001, 2002), IARC (2001), IPCS (1997), Euro Chlor (2005), HCN (2011), NTP (2011), JRC (2012), the references cited in these reviews and a literature update (time period 2002-2012).

1. Substance identification, physico-chemical properties

Name: Hexachlorobenzene
Synonyms: HCB, perchlorobenzene, pentachlorophenyl chloride
Molecular formula: C_6Cl_6
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): $1.1–2.3 \times 10^{-3}$ kPa
Conversion factors: 1 ppm = 11.8 mg/m^3
(20 °C, 101.3kPa) 1 mg/m^3 = 0.08 ppm

EU harmonised classification:

Carc. 1B (H350)	H350	May cause cancer
STOT RE 1	H372	Causes damage to organs
Aquatic Acute 1	H400	Very toxic to aquatic life
Aquatic Chronic 1	H410	Very toxic to aquatic life with long lasting effects

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

cold alcohol and 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. Occurrence/use and occupational exposure

2.1. Occurrence/use

Hexachlorobenzene is a chlorinated hydrocarbon industrial chemical and one of the most persistent environmental pollutants due to its chemical stability and resistance to biodegradation. Hexachlorobenzene has been banned globally under the Stockholm Convention (2001). It was widely used as a fungicide until 1965/1970s. Further uses were fireworks, ammunition and synthetic rubber. Hexachlorobenzene accumulates in the environment, animals and humans. Although hexachlorobenzene is not currently manufactured as a commercial end product, hexachlorobenzene is still formed as a by-product during the manufacture of other chlorine containing compounds (e.g. chlorinated solvents like tri- and tetrachloroethylene) and chlorinated pesticides.

Bailey *et al* (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 1 270 kg/year (Bailey 2001). Current estimations of hexachlorobenzene as a by-product or impurity were not available.

2.2. Exposure

2.2.1. General population

Due to its previous use as a fungicide, hexachlorobenzene occurs in significant amounts in the atmosphere, the surface waters and the terrestrial environment. Because of its persistent and bioaccumulative nature, it stays in the environment for a long time and contaminates the food chain and can still be detected in the blood of the general population, despite its ban more than 30 years ago. The general population may be exposed to very low concentrations of hexachlorobenzene through ingestion of contaminated drinking water and food, from contaminated ambient air and contact with contaminated soil or at the workplace (Section 2.2.2) (ATSDR 2002). The greatest exposure source is fish caught from contaminated water or residing near former manufacturing or waste-disposal sites (NTP 2011).

In the US, the calculated yearly intake from drinking water contaminated with hexachlorobenzene is 0.00085 µg/kg bw; exposure to contaminated food is calculated to result in an average yearly uptake of 1 µg/kg bw. An average yearly intake of 0.01 µg/kg bw has been estimated for exposure from contaminated air (ATSDR 2002). In 2000, in a population of Catalonia, Spain, the dietary intake of hexachlorobenzene by contaminated food was estimated to be 0.0025 and 0.0024 µg/kg bw in male and female adults (Falcó *et al* 2004). Further studies in Spain, Germany and Sweden showed a continuous reduction in hexachlorobenzene intake since its use was forbidden (Angerer *et al* 2003, Martí-Cid *et al* 2008, Hardell *et al* 2010). In Spain, for example, a reduction in the intake of more than 50 % in male adults was seen between the years 2000 and 2006 (Martí-Cid *et al* 2008). Biological monitoring has

been extensively used to assess the exposure of the general population to hexachlorobenzene. These data are presented in Section 3.1.1.

2.2.2. Occupational exposure

Although all uses of hexachlorobenzene as a pesticide has 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 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).

2.2.3. Measurement techniques and analytical methods

ATSDR (2002) and IARC (2001) summarised several analytical methods. Determination of hexachlorobenzene in air and in biological materials, generally consists 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).

Measurement techniques have been developed for the determination of hexachlorobenzene in air, whole blood or serum/plasma, urine, faeces, adipose tissue and breast milk (ATSDR 2002, Angerer *et al* 2003, Angerer *et al* 1991, IARC 2001).

Detection limits for air levels depend on the amount of air sampled, but are usually in the ppb range or lower (ATSDR 2002). US EPA (1988) reports a detection limit of 5 ng/m^3 for the analysis of air hexachlorobenzene levels using polyurethane foam

adsorbent, Soxhlet extraction, concentration phase and analysis by dual column megabore GC/ECD or GC/ECD and GC/MS.

3. Health significance

3.1. Toxicokinetics

No data on absorption at inhalation exposure were available. Dermal absorption in rats was 0.9 µg/cm^2/hour (Greim 2001, HCN 2011). Human oral absorption is up to 85 % and decreases at higher blood concentration of hexachlorobenzene (Euro Chlor 2005, HCN 2011). Absorbed hexachlorobenzene distributes into 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).

3.1.1. 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 (ATSDR 2002, Angerer *et al* 2003, Angerer *et al* 1991, IARC 2001). Since hexachlorobenzene exists in erythrocytes only in insignificant amounts, higher concentrations can be detected when plasma/serum is used. 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 ng/ml with concentrations up to 4 ng/ml in Germany and Iceland. However, in Portugal and Spain elevated values with a maximum of 124 ng/ml were reported.

In 1999, German reference values for adults in whole blood ranged from 0.4–4.0 µg/l (Angerer *et al* 2003). In 2003, reference values were 0.12–1.19 µg/l dependent on the age (UBA 2003), the mean concentration being 0.44 µg/l and a 95th percentile for 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 hexachlorobenzene 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, US EPA 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.

3.2. Acute toxicity

3.2.1. Human data

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

3.2.2. Animal data

In animals, hexachlorobenzene has a low acute toxicity. Oral LD_{50} values range from 100 mg/kg bw in cats up to 3 500–10 000 mg/kg bw in rats. The inhalation LC_{50} 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).

3.3. Irritancy and corrosivity

3.3.1. Human data

No data were available.

3.3.2. 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.

3.4. Sensitisation

3.4.1. Human data

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

3.4.2. Animal data

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

3.5. Repeated dose toxicity

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).

3.5.1. 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 & 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 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 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 75 male and 11 female factory workers. In males, all abnormal T4 and γ-GT levels (below or above reference limits, respectively) were in factory workers (Sala *et al* 2001). Adjustment of the results for alcohol consumption, sex, age, body mass index (BMI), recent weight loss and smoking did not affect the results.

Currier *et al* (1980) reported health surveillance data from 50 workers from the production of chlorinated solvent 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), haemoglobin and haematocrit).

In the MAK BAT-documentation (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 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: $C_{ss} = 1.44 \times T_{½} \times D/V_d \times t$, where $T_{½}$ (half-time) is 6 years (2 190 days), V_d (volume of distribution) is 7 l/kg, and t (dosing interval) is 1 day. Using this formula, a plasma level of 150 µg/l is estimated to correspond to a daily dose of 0.33 µg/kg bw/day. This can be further estimated to correspond to an inhaled dose of 2.2 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 and equal absorption via inhalation and the oral route).

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.

3.5.2. Animal data

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

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 (Bourque et *al* 1995, Jarrell *et al* 1993, Babineau *et al* 1991, 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 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).

Degenerative changes in the liver occurred at 0.8 mg/kg bw/day in a 2-generation study with rats, 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 1 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, 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 inhalatory and oral route) of 0.006 mg/m^3.

3.6. Genotoxicity

3.6.1. In vitro

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

3.6.2. In vivo – human data

A micronucleus test with human peripheral lymphocytes of hexachlorobenzene exposed workers, 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).

3.6.3. In vivo – animal data

Hexachlorobenzene did not induce single-strand breaks or formation of 8-hydroxydeoxyguanosine in the liver of mice, and the observed increase in replicative DNA-synthesis in mice was not dose-dependent (Greim 2001).

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

3.7. Carcinogenicity

3.7.1. 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, 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.

3.7.2. 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 a tumour-promoting effect (Greim 2001, HCN 2011, NTP 2011).

3.8. Reproductive toxicity

3.8.1. Human data

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 effects of hexachlorobenzene on human fertility were available.

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). Thus, human epidemiological studies are insufficient for an evaluation of developmental toxicity.

3.8.2. Animal data

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 two dominant-lethal tests in rats up to 60 mg/kg bw/day or 221 mg/kg bw/day (Arnold *et al* 1985, 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 (Bourque *et al* 1995, Jarrell *et al* 1993, Babineau *et al* 1991, Sims *et al* 1991).

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 neuro-developmental 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, 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.

4. Recommendation

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-live. 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 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 seen. 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 other studies, 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 13-week studies 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. 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). 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

Due to e.g. differences related to toxicokinetics, extrapolation from animal data to human occupational exposure involves several uncertainties. However, based on human data 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* based on the available human data. Although lipid levels in plasma/serum may cause some variation in measured hexachlorobenzene levels, their influence at these hexachlorobenzene plasma/serum levels is considered to be of minor importance. Because of the long half-time of hexachlorobenzene, sampling time is not critical for the interpretation of biomonitoring results.

No OEL is recommended. Because of the highly cumulative nature of hexachlorobenzene, correlations between air and blood/plasma levels of hexachlorobenzene have been poor, and biomonitoring is the recommended method to measure cumulative exposure.

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 average dermal absorption rate of hexachlorobenzene in rats was calculated as 0.9 ± 0.2 µg/cm^2/hour (HCN 2011). 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.

The present Recommendation was adopted by SCOEL on Date Month Year.

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