# Hexachlorobenzene

| CAS number: | 118-74-1 |
| --- | --- |
| Synonyms: | Amatin, anticarie, HCB, hexachlorobenzol, pentachlorophenyl chloride, perchlorobenzene, sanocide |
| Chemical formula: | C6Cl6 |
| Structural formula: | — |

Workplace exposure standard (new)

| TWA: | **0.002 mg/m3** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc. 1B, Sk.** |
| IDLH: | **—** |
| **Sampling and analysis:** There is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.002 mg/m3 is recommended to protect for porphyria, liver toxicity and fertility effects in exposed workers. This concentration is sufficiently low to also protect for potential threshold-based carcinogenic effects in exposed workers.

## Discussion and conclusions

Hexachlorobenzene (HCB) is mainly used as a fungicide on grains. It is also used in additive polymers (such as polyvinyl chloride), for pyrotechnic compositions for military purposes and as a porosity controller in the manufacture of electrodes.

Critical effects of exposure include porphyria, neurotoxicity and fertility effects (ACGIH, 2018; HCOTN, 2011; SCOEL. 2016). HCB is carcinogenic in animals through a threshold mechanism related to general liver toxicity. As such, preventing liver toxicity is likely to prevent the formation of cancer.

No adverse health effects were seen in workers with blood levels of 312 ppb. This was calculated as corresponding to an equivalent eight-hour TWA inhalation of 2.9 µg/m3 (ACGIH, 2018). HCOTN (2011) reported a NOAEL of 0.01 mg/kg/day for fertility effects in monkeys from a sub-chronic feeding study as the basis for its recommended TWA of 0.006 mg/m3. HCOTN adjusted the NOAEL by 12 to account for the lack of chronic data and applied generic kinetic conversion factors (HCOTN, 2011). ACGIH (2018) based its TWA of 0.002 mg/m3 on a NOAEL of 0.033 mg/kg/day identified in an 18‑month study in monkeys for effects on haematology, serum hormone levels and urinary porphyrin levels and applied an uncertainty factor of 100. This value was further supported to be protective of porphyria cutanea tarda (PCT) and liver effects as demonstrated by a reported NOAEL of 0.05 mg/kg/day in pigs (ACGIH, 2018). It must be noted that extrapolation from animal studies to humans carries significant uncertainties due to difference in half-lives between animals and humans (DFG, 1998).

A TWA of 0.002 mg/m3 by ACGIH (2018) is recommended to be adopted. This recommendation is considered suitable given the duration of the underlying study, the uncertainty factor applied to account for interspecies differences and is supported by the calculated no effect level in workers. This TWA is expected to be protective for porphyria, liver toxicity and fertility effects.

## Recommendation for notations

Classified as a category 1B carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended based on evidence of significant dermal uptake in animals, the contribution to total uptake and the severity of potential systemic effects.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| ***SWA NA*** |
| No report. |
| ACGIH 2001 TLV-TWA: 0.002 mg/m3 |
| TLV-TWA recommended to minimise the potential for increased formation and excretion of porphyrins (porphyrogenicity) leading to dermal lesions and ulcerations, neurotoxicity and possible liver cancer reported in animals.  Summary of data:   * Stated 3 toxic effects of interest: carcinogenicity, neurotoxicity, porphyrogenicity.   Human data:   * No reports on human exposure by inhalation identified * In a case report, 348 cases of acquired toxic PCT (skin disorder) after ingesting contaminated seed grain; 25 yr and >30 yr follow-up report: * 3,000–4,000 humans exposed at about 10 mg/kg/d for up to 3 yr * 10% died and about 100 people still displayed adverse health effects * daily dose corresponded to a cumulative dose of 10,950 mg/kg * those exposed had the same spectrum of adverse effects as animals at similar exposure levels, except for cancer * Workers with blood levels of 160–312 ppb had no adverse health effects * Human exposure theoretically linked to porphyria and cancer * A case report regarding industrial exposure and the occurrence of hepatocellular carcinoma in a worker; further research recommended to clarify this possible relationship.   Animal data:   * Occlusive application of 10 mg/kg dose in rats; 1% absorbed in 6 h; 10% absorbed in 72 h; absorption described as a first-order process * Increases incidence of liver tumours in mice and hamsters fed 4–6 mg/kg/d for their lifetime * NOEL of 0.05 mg/kg/d in pigs; 0.05, 0.5, 5 or 50 mg/kg/d 90 d feeding study; PCT at 50 mg/kg; induction of microsomal liver enzymes and increased liver weight at 5 mg/kg * NOEL of 0.033 mg/kg/d in monkeys; did not affect serum hormone levels, urinary copro- and uroporphyrin levels or haematology; 18 mo study; route not disclosed * Rodents and primates do not metabolise HCB well; indicating the parent compound is responsible for adverse effects; half-life in rhesus monkey estimated to be 2.5-3 yr.   Not genotoxic either *in vivo* or in the Ames tests.  Reported to penetrate the intact skin in significant quantities warranting skin notation.  Insufficient data to recommend a sensitiser notation or TLV-STEL.  TWA basis:   * TLV-TWA based on NOEL of 0.033 mg/kg/d reduced by uncertainty factor of 100 to 0.33 µg/kg/d * 70 kg worker inhaling 10 m3 of air per 8 h shift assuming 100% absorption; yields a TWA of 2.31 µg/m3 * Supported by blood level of 312 ppb corresponding to daily dose at steady state of 0.42 µg/kg/d; TWA inhalation equivalent to a concentration of 2.9 µg/m3 assuming 70 kg worker inhaling 10 m3 of air per 8 h shift and 100% absorption. |
| DFG 1998 Not assigned |
| Summary of additional data:   * Database considered insufficient or unreliable to confidently derive MAK * Extrapolation from animal studies to human exposure associated with significant uncertainty due to different half-lives in human and animals; ≈5 mo in rats; 2.5–3 yr in monkeys; >2 yr in humans * Liver, bile duct and kidney tumours observed in experimental animals; mechanism likely cytochrome P450-mediated formation of oxygen radicals resulting in cell damage and subsequent compensatory hyperplasia. |
| SCOEL 2016 Not assigned |
| Summary of additional data:   * No OEL recommended because measurement in air may grossly underestimate total exposure due to: * low vapour pressure * potential for significant skin absorption and * cumulative nature of HCB exposure * Skin absorption rate of 0.9 µg/cm2/h in rats * NOAEL of 0.01 mg/kg/d; oral 13 wk study in monkeys used as starting point for rescinded TWA OEL of 0.006 mg/m3 * Conclusion that mechanism of carcinogenicity is threshold based and related to the general liver toxicity; preventing liver toxicity is likely to prevent cancer. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2011 TWA: 0.006 mg/m3 |
| Recommended health-based OEL cited as protective of fertility and liver effects identified in animals.  Summary of additional data:   * Insufficient data in humans to derive TWA * Inhalation study in animals not suitable to derive TWA * 13 wk oral study in monkeys: * NOAEL of 0.01 mg/kg/d for fertility effects (necrosis of ovary surface epithelium cells) * NOAEL of 0.1 mg/kg/d for liver histopathology * LOAEL 0.1 mg/kg/d for degenerative lesions in ovarian follicles * TWA derived from NOAEL of 0.01 mg/kg/d: * application of an uncertainty factor of 12 for extrapolation from sub-chronic to chronic exposure and intra- and interspecies uncertainty results in 0.0008 mg/kg/d * conversion of the oral to inhalational exposure assuming 70 kg worker inhaling 10 m3 results in 0.006 mg/m3 * Considered protective of hepatotoxic effects based on comparison of above calculation and substituting the NOAEL of 0.05 mg/kg/d in pigs for hepatotoxicity and the lowest dose at which toxicity in humans was observed 0.8 mg/kg/d (liver and other tissues and organs). |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| US EPA |  | 1988 | * NOAEL of 0.08 mg/kg/d in rats for liver effects; chronic feeding study * Oral slope factor of 1.6 per mg/kg/d (carcinogenic risk); calculated to a minimal risk inhalation of 0.0003 mg/m3 (0.3 ppb). |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | No |
| --- | --- |
| **The chemical is not a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations |
| --- | --- |
| SWA | NA |
| HCIS | Carcinogenicity – category 1B |
| NICNAS | NA |
| EU Annex | Carcinogenicity – category 1B |
| ECHA | Carc. 1B |
| ACGIH | Carcinogenicity – A3, Skin |
| DFG | Carcinogenicity – 4, H (skin) |
| SCOEL | Skin |
| HCOTN | — |
| IARC | Carcinogenicity – Group 2B |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | Adverse effects in human case study: |  |  |  | |  | Dermal LD50 ≤1000 mg/kg: |  |  |  | |  | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | |  | Dermal LD50/Inhalation LD50 <10: |  |  |  | |  | *In vivo* dermal absorption rate >10%: |  |  |  | |  | Estimated dermal exposure at WES >10%: | Yes | 2.00 |  | |  |  | **insufficient data to assign a skin notation** | | | |

### IDLH

| Is there a suitable IDLH value available? | No |
| --- | --- |

## Additional information

| Molecular weight: | 284.80 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 11.6 mg/m3; 1 mg/m3 = 0.09 ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2001) Hexachlorobenzene – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2016) Recommendation from the Scientific Committee on Occupational Exposure Limits for HEXACHLOROBENZENE. SCOEL/REC/188.

European Chemicals Agency (ECHA) (2019) Hexachlorobenzene – REACH assessment.

Health Council of the Netherlands (HCOTN) (2011) Hexachlorobenzene. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2011/35.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).