

HEXACHLOROBUTADIENE

CAS: 87-68-3

HCBD; Hexachloro-1,3-butadiene

C₄Cl₆

Cl₂C=CCl-CCl=CCl₂

Skin

TLV-TWA, 0.02 ppm (0.21 mg/m³)

A2 - Suspected Human Carcinogen

1980: TLV-TWA, 0.02 ppm, A2 Carcinogen, proposed

1982-present: TLV-TWA, 0.02 ppm, A2 Carcinogen

1984-present: Skin notation

1992: Documentation revised

Chemical and Physical Properties

Hexachlorobutadiene (HCBD) is a heavy, clear liquid. Chemical and physical properties include:⁽¹⁾

Molecular weight: 260.76

Melting point: -21°C

Boiling point: 212°C

Solubility: insoluble in water; soluble in alcohol and diethyl ether

Major Uses or Sources of Occupational Exposure

Although HCBD has been employed as a pesticide with limited applications, it is primarily encountered as a by-product of certain processes associated with the chlorination of hydrocarbons. It is used as a solvent for elastomers, heat transfer liquid, transformer and hydraulic fluid, and a wash liquor for removing C₄ and higher hydrocarbons.⁽¹⁾

Animal Studies

Acute

The acute oral toxicity of HCBD is rated by various investigators as moderate to high; LD₅₀ values have been reported as 90 mg/kg for guinea pigs;⁽²⁾ 87-116 mg/kg for mice;^(3,4) and 200-350 mg/kg for rats.^(3,4) The lethality of HCBD following single, oral doses indicated that young rats are more sensitive than adults. The LD₅₀ in 21-day-old male and female mice was 64 and 46 mg/kg, respectively. Some deaths were delayed as long as 17 days after dosing, but the majority of these mice died on the second or third day post-treatment.⁽⁵⁾ The material is absorbed through the skin of rabbits according to Kociba et al.⁽⁵⁾ The dosages causing death by dermal absorption are in the same range as by oral administration.

The mortality following single exposures to HCBD vapors has been described.⁽⁵⁾ Some or all of the rats exposed for 4 to 7 hours at 133 to 500 ppm died. All rats

survived 161 ppm for 0.88 hour or 34 ppm for 3.3 hours. Most guinea pigs and cats died subsequent to inhalation of 161 ppm for 0.88 hours or 34 ppm for 7.5 hours.⁽⁵⁾

Subchronic

Gage⁽⁶⁾ described short-term repeated inhalation studies of HCBD using groups of four male and four female rats and summarized the findings as follows:

- 250 ppm: 2 x 4-hour exposures — ocular and upper respiratory tract irritation; respiratory difficulty, females affected more than males, apparent recovery after exposure; histopathologic study showed degeneration of the middle renal proximal tubules and of the adrenal cortex.
- 100 ppm: 12 x 6-hour exposures — ocular and upper respiratory tract irritation; respiratory difficulty; poor condition; weight loss; slight anemia in females; urine tests normal, two females died; gross inspection showed kidneys pale and enlarged, adrenals enlarged; degeneration of renal cortical tubules with epithelial regeneration were documented with histopathologic study.
- 25 ppm: 15 x 6-hour exposures — poor condition; diminished weight gain in females; respiratory difficulty; blood and urine tests normal; at gross necropsy, the kidneys were pale and enlarged; microscopic evaluation revealed damage to the renal proximal tubules.
- 10 ppm: 15 x 6-hour exposures — retarded weight gain in females; at gross autopsy, all of the organs examined were reported to be normal.
- 5 ppm: 15 x 6-hour exposures — no signs of toxicity, and upon gross inspection of these rats, all of the organs were reported to be normal.

Gulko et al.⁽⁴⁾ reported that repeated inhalation exposure at 24 mg HCBD/m³ (about 2.3 ppm) for 7 months caused no alterations in mice or rats. The duration and frequency of the repeated exposures were not stated.

No deleterious effects were reported by Schwetz et al.⁽⁷⁾ in adult Japanese quail maintained for 90 days on diets containing up to 30 ppm HCBD by weight (about 5 mg/kg/day).

Feeding HCBD in the diet of rats at daily doses ranging from 1 to 100 mg/kg for 30 days was reported to increase the kidney-to-body weight ratio and induce renal tubular degeneration, necrosis, and regenerative hyperplasia in the rats fed 30, 65, or 100 mg HCBD/kg/day. Other adverse effects observed included decreased food consumption and body weight gain at 10, 30, 65, and 100 mg/kg/day; minimal hepatocellular swelling at 100 mg/kg/day; and hemoconcentrations at 10, 30, 65, and 100 mg/kg/day. No adverse effects were observed among those receiving 3 mg/kg/day. The kidney was the organ most sensitive to the deleterious effects of HCBD.

Chronic/Carcinogenicity

Detailed data on the results of the lifetime dietary study of HCB in rats are available in a report by Kociba et al.⁽⁶⁾ Kociba et al. have summarized these data as follows:⁽⁵⁾

Lifetime ingestion of the highest dose level of 20 mg/kg-day of HCB caused multiple toxicologic effects. This included increased mortality (males), decreased body weight gain (males and females), increased urinary excretion of coproporphyrin (males and females), and increased terminal weights of kidneys (males and females).

Pathologic examinations revealed changes in the kidneys, including hyperplasia and neoplasia of renal tubular epithelium. Some of the neoplasms were noted grossly as nodules in the kidneys. These nodules in the kidneys were microscopically diagnosed as renal tubular adenomas or adenocarcinomas, some of which metastasized to the lungs. Approximately 23% of the males and 25% of the females from the 20 mg/kg/day dose level had renal tubular neoplasms.

At the intermediate dose level of 2.0 mg/kg-day of HCB, findings considered related to treatment were limited to an increased urinary excretion of coproporphyrin (females only) and increased hyperplasia of renal tubular epithelium. This intermediate dose level of 2 mg/kg-day of HCB caused no neoplasms considered related to treatment. Lifetime ingestion of the lowest dose level of 0.2 mg/kg-day of HCB caused no discernible ill effects in any of the parameters monitored in this study.⁽⁵⁾

Kociba and associates⁽⁵⁾ concluded that "... these data indicate a clear-cut dose-response relationship for HCB-induced toxicity affecting primarily the kidney. HCB-induced renal neoplasms occurred only at a dose level higher than that causing discernible renal injury."

Reproductive/Developmental

Kociba⁽⁵⁾ reviewed the reproductive and developmental toxicity studies carried out by Schwetz et al.⁽⁹⁾ as follows:

Adult male and female rats ingesting the high dose level of 20 mg/kg-day of HCB showed multiple toxicological effects, including decreases in food consumption and body weight gain. Terminal kidney weights of these males and females were increased, as were the liver weights of the males. Pathologic examination revealed renal tubular epithelial degeneration and regeneration in both males and females ingesting 20 mg/kg-day of HCB. Adult rats ingesting the intermediate dose level of 2 mg/kg-

day of HCB were comparable to controls except for a much lower incidence of the renal tubular histopathologic changes noted at the high dose level. Adult rats ingesting 0.2 mg/kg-day of HCB had no observations considered related to treatment.

The ingestion of 20, 2, or 0.2 mg/kg-day of HCB had no effect on the percent pregnancy, gestated survival, neonatal survival, neonatal sex ratio or morphologic alterations in neonates. Neonatal body weights were unaffected except for a decreased body weight on day 21 for the neonates of the high dose level, 20 mg/kg-day of HCB.

TLV Recommendation

Based on a no-effect level of 0.2 mg/kg/day after continuous ingestion of HCB by rats for 2 years, a TLV-TWA of 0.02 ppm is recommended. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA, even when the 8-hour TWA is within the recommended limits. Since Kociba et al.⁽⁵⁾ reported that HCB is absorbed through rabbit skin in amounts comparable to those absorbed following oral administration, this substance merits the skin notation.

Since a significant carcinogenic response resulted from ingestion of less than 50 mg/kg/day,⁽⁷⁾ HCB can be considered a rodent carcinogen of intermediate potency. Accordingly, HCB has been given the A2 designation, suspected human carcinogen.

Other Recommendations

OSHA PEL: OSHA established a PEL-TWA of 0.02 ppm for HCB (with no skin notation). OSHA concluded that the PEL would protect workers exposed to this substance from the significant risks of kidney damage; eye, skin, and pulmonary irritation; and renal neoplasms.⁽¹⁰⁾

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N6A] established a REL-TWA of 0.02 ppm with a skin notation by concurrence with the original OSHA proposed PEL and recommended that OSHA consider HCB as a potential occupational carcinogen.⁽¹⁰⁾ NIOSH has not established an IDLH value for this substance.

ACGIH Rationale for TLVs that Differ from the PEL or REL: The TLV, PEL, and REL values are identical save for the skin designation. Although no quantitative data are cited, Kociba et al.⁽⁵⁾ reported that HCB is absorbed in toxicologically significant amounts through the skin of

rabbits. Based on the low TLV, even small quantities of HCBD absorbed through the skin would contribute significantly to the body burden. The fact that HCBD is currently classified as A2 (suspected human carcinogen) also merits attention. Based on the above, ACGIH believes HCBD merits a skin notation.

NTP Studies: NTP has conducted a prechronic feeding study in mice at 0, 1, 3, 10, 30, or 100 ppm of HCBD. A July 1992 NTP status report on this study does not indicate a carcinogen designation at this time. This substance has also been selected for study by inhalation. Chemical disposition and pharmacokinetic studies have been completed by NTP. The chemical was negative in the *Salmonella* assay, the *Drosophila* test for sex-linked recessive lethal mutations, and for the induction of chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells. HCBD was positive for the induction of sister-chromatid exchanges in the CHO assay and was tested in the mouse lymphoma assay.

Carcinogenic Classification

IARC: Group 3, not classifiable as to its carcinogenicity to humans.

MAK: Group B, justifiably suspected of having carcinogenic potential.

NIOSH: Carcinogen, with no further categorization.

TLV: A2, suspected human carcinogen.

Other Nations

Australia: 0.02 ppm, skin, Category 3, suspected of

having carcinogenic potential (1990); Federal Republic of Germany: no MAK, skin, Group B, justifiably suspected of having carcinogenic potential (1991).

References

1. Sax, N.I.; Lewis, Sr., R.J.: *Hawley's Condensed Chemical Dictionary*, 11th ed., p. 596. Van Nostrand Reinhold Co., New York (1987).
2. Murzakaev, F.G.: Toxicity Data for Hexachlorobutadiene and its Intermediate. *Fannakol, Toksikol* 26:750 (1963); *Chem. Abstr.* 60:13776b (1964).
3. Gehring, P.J.; MacDougall, D.: Review of the Toxicity of Hexachlorobenzene and Hexachlorobutadiene. *Toxicology Research Laboratory, Dow Chemical Company, Midland, MI* (1971).
4. Gulko, A.G.; Zimina, N.I.; Shroit, I.G.: Toxicological Study of the Insecticide Hexachlorobutadiene. *Vopr. Gig. Sanit. Ozdorovl. Vneshn. Sredy. Kishinev. Sb.* 128 (1964); *Chem. Abstr.* 62:13753c (1965).
5. Kociba, R.J.; Schwetz, B.A.; Keyes, D.G.; et al.: Chronic Toxicity and Reproduction Studies of Hexachlorobutadiene in Rats. *Environ. Health Perspect.* 21:49-53 (1977).
6. Gage, J.C.: The Subacute Inhalation Toxicity of 109 Industrial Chemicals. *Br. J. Ind. Med.* 27:1-18 (1970).
7. Schwetz, B.A.; Norris, J.M.; Kociba, R.J.; et al.: Reproduction Study of Japanese Quail Fed Hexachlorobutadiene for 90 Days. *Toxicol. Appl. Pharmacol.* 30:255-265 (1974).
8. Kociba, R.J.; Keyes, D.G.; Jersey, G.C.; et al.: Results of a Two-year Chronic Toxicity Study with Hexachlorobutadiene in Rats. *Am. Ind. Hyg. Assoc. J.* 38:589-602 (1977).
9. Schwetz, B.A.; Smith, F.A.; Humiston, C.G.; et al.: Results of a Reproduction Study in Rats Fed Diets Containing Hexachlorobutadiene. *Toxicol. Appl. Pharmacol.* 42:387-398 (1977).
10. U.S. Department of Labor, Occupational Safety and Health Administration: 29 CFR Part 1910, Air Contaminants; Final Rule. *Fed. Reg.* 54(12):2489-2490 (January 19, 1989).