

LINDANE

CAS number: 58-89-9

Synonyms: Gamma-benzene hexachloride, gamma-BHC, gamma-HCH, gamma-hexachlorohexane

Chemical formula: $C_6H_6Cl_6$

Structural formula: —

Workplace exposure standard (retained)

TWA: 0.008 ppm (0.1 mg/m³)

STEL: —

Peak limitation: —

Notations: Sk.

IDLH: 50 mg/m³

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 0.008 ppm (0.1 mg/m³) is recommended to protect for liver damage and potential central nervous system disturbances in exposed workers.

Discussion and conclusions

Lindane is a stereoisomer of hexachlorocyclohexane (HCH) and was formerly used as an insecticide and an ingredient in wood preservatives. Technical grade Lindane contains mixtures of other HCH isomers. Critical effects are liver damage caused by oxidative stress, which may promote tumorigenicity; the technical grade substance has higher carcinogenic potential than Lindane alone (ACGIH, 2018; US EPA, 1987).

Available human inhalational data are confounded by mixed exposures to other pesticides and high dermal exposures, but show increased levels of oxidative stress markers in exposed workers (DFG, 2001). A NOAEC of 0.6 mg/m³ for mild changes in clinical parameters and increased oxidative stress responses is reported in rats and is consistent with human data (DFG, 2001). A NOAEC of 0.19 mg/mg³ for slight histological changes is also reported from a chronic rat inhalation study (ACGIH, 2018). Lindane-induced oxidative stress is also associated with tumour promotion capacity in the presence of known tumour initiators (DFG, 2001).

A TWA of 0.1 mg/m³, as derived by DFG (2001), is recommended to be adopted and is expected to be protective of liver damage, including tumorigenicity, induced by oxidative stress. Based on the weight of evidence presented in workplace and animal inhalation studies, the margin of safety provided by the recommendations of ACGIH (2018) and the administrative OEL presented by HCOTN (2001) is considered insufficient.

A re-evaluation of the carcinogenic potential should be prioritised in subsequent reviews due to equivocal evidence for carcinogenicity in humans. HCOTN (2001) considers the evidence from animal

studies insufficient for classification. However, recent assessments by ACGIH (2018) and IARC (2018) support a carcinogenicity notation based on evidence in animals and humans, respectively, which is inconsistent with the entry found in the HCIS database.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). However, inconsistencies in carcinogenicity notations were found in the source material during the current evaluation. A review of carcinogenicity classification is recommended.

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

A skin notation is recommended based on evidence for dermal absorption and adverse systemic effects in humans.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 0.008 ppm (0.1 mg/m³)
ACGIH	2001	TLV-TWA: 0.5 mg/m³
<p>TLV-TWA intended to protect for CNS disturbances.</p> <p>Summary of data:</p> <p>Lindane is a stereoisomer of 1,2,3,4,5,6-hexachlorocyclohexane (HCH); technical mixtures comprise Lindane and other stereoisomers of HCH. TLV-TWA based on NOAEL of 0.19 mg/m³ and of LOAEL 0.7 mg/m³ for CNS effects in chronically exposed animals; derivation not discussed.</p> <p>Human data:</p> <ul style="list-style-type: none"> • Rapidly appears in blood and peaks after 6 h following 0.3–1% topical application in volunteers; measured in breast milk of exposed women (no further details provided) • Accidental overexposures <i>via</i> inhalation resulted in anaemia, severe reduction in white blood cells, or vomiting, convulsions and acute renal failure following ingestion • Patients tolerated 40 mg/kg/d of pure Lindane, but technical grade substance caused diarrhoea, vertigo and headache at this concentration (14 d) • Electroencephalogram (EEG) disturbances in exposed male workers with blood Lindane levels of 0.002–0.340 ppm; frequency of clinical and EEG changes in those with blood concentrations >0.02 ppm (n=37, 2 yr exposure, air concentrations not specified); 22/37 workers had been exposed to Aldrin previously • Topical lotions containing 1% Lindane associated with poisoning following application. <p>Animal data:</p> <ul style="list-style-type: none"> • Dermal LD₅₀: 500–1,000 mg/kg (rats), 300 mg/kg (rabbits): <ul style="list-style-type: none"> ◦ exposure caused diarrhoea, hypothermia, nose bleeds, and convulsions (rats) • 80% absorbed intestinally if administered in oil, only 6% if administered as aqueous suspension; distributed to adipose tissue, peak concentrations reached after 2–5 d and eliminated after 1 wk following exposure cessation (rats): <ul style="list-style-type: none"> ◦ non-oral doses excreted in faeces (34%) and urine (5%) • NOAEL: 0.19 mg/m³ for histopathological changes (not specified) in chronic inhalation study (rats, 24 h/d, 7 d/wk, 655 d): <ul style="list-style-type: none"> ◦ LOAEL of 0.7 mg/m³ for minimal pathology (no further details provided) reported in similar study with several unspecified test species (7 h/d, 5 d/wk, 1 yr) • Liver tumours reported at 660 mg/kg/d of technical grade Lindane in repeat feeding study (male mice, 24 wk); no cancers reported in lower dose groups 6.6 or 66 mg/kg/d: <ul style="list-style-type: none"> ◦ similar results in 80 wk feeding study at 80 and 160 ppm of diet (mice) • Foetal and maternal NOAEL of 0.05 mg/kg/d for lengthened gestation, decreased number of foetuses and foetal growth • Most mutagenicity studies indicate no potential for genotoxicity except for positive result in 1 dominant lethal mutation assay with 65 mg/kg/d technical grade Lindane (mice, 4–8 mo). <p>Insufficient data to recommend a STEL or sensitiser notation.</p> <p>A skin notation is warranted based on reports of systemic toxicity from dermal contact in humans. Carcinogenicity demonstrated in chronically fed animals, relevance to humans however unknown.</p>		



Source	Year set	Standard
DFG	1998	MAK: 0.1 mg/m³
<p>Summary of additional data:</p> <p>MAK intended to protect for adverse liver effects, including tumorigenicity, and immune system toxicity. Liver tumour promoting activity likely due to cytochrome P450 mediated monooxygenase induction. Evidence for increased monooxygenase activity, but no adverse clinical effects, in workers exposed at 0.004–0.15 mg/m³ is confounded by excess dermal absorption. NOAEL of 0.6 mg/m³ for monooxygenase induction in rats therefore used as line of evidence in MAK evaluation. Based on consistency of monooxygenase induction in workplace study with animal inhalation data, MAK of 0.1 mg/m³ expected to be protective of adverse liver effects including tumorigenicity.</p> <p>Positive carcinogenicity in mice and insufficient data for carcinogenic activity in humans warrants a category 4 notation. Uptake through human skin can exceed inhalational intake at the MAK, skin notation therefore recommended. A BAT of 25 µg/L of plasma or serum is recommended.</p> <p>Human data:</p> <ul style="list-style-type: none"> Seminal fluid concentrations of 18.64 µg/L associated with increased ROS, and decreased sperm motility and concentration; another chlorinated insecticide present in exposure was a confounding factor Increased odds ratio (1.5) for development of non-Hodgkin's lymphoma in farmers exposed to various pesticides, contribution of Lindane to this increased risk is unclear but is not ruled out Increased risk of non-Hodgkin's lymphoma associated with exposure to HCH isomeric mixtures, but insufficient data to associate risk to Lindane isomer alone No adverse effects to neurological status, clinical chemistry, or haematology in production workers exposed at 0.004–0.15 mg/m³ with average serum concentration 36.9 µg/L; some workers were dermally exposed to large amounts of solid substance, which prevents correlation of air and serum concentrations <p>Animal data:</p> <ul style="list-style-type: none"> Oxidative stress responses and increased generation of ROS related to immunotoxicity in animals, and possibly explains increased risk of non-Hodgkin's lymphoma in humans Mild transient clinical effects including increased liver cytochrome P450 levels, diarrhoea, and ruffled coat at 4.5 mg/m³ (rats, 6 h/d, 7 d/wk, 3 mo): <ul style="list-style-type: none"> NOAEL: 0.6 mg/m³ similar study reported NOAEL: 1 mg/m³ for histopathological changes to liver, but 2 animals died inexplicably at this exposure (mice, 6 h/d, 5 d/wk, 13 wk); NOAEL for this unexplained mortality was 0.3 mg/m³ Reduced immune response to foreign erythrocytes at 6 mg/kg/d in repeat feeding study (mice, 12 wk); NOAEL: 2 mg/kg/d <ul style="list-style-type: none"> similar study with reported NOAEL: 0.25 mg/kg/d and LOAEL: 1.8 mg/kg/d (rats, 22 wk); immune response challenged with tetanus toxoid Immune system suppression at 0.012 mg/kg/d in repeat feeding study (mice, 24 wk); no NOAEL determined in study, results not considered in evaluation due to inconsistencies with LOAEL presented in other studies and insufficient experimental documentation Liver tumour promotion at 2.5 mg/kg/d when co-administered with <i>N</i>-nitrosomorpholine initiator in repeat feeding study, dose groups: 0, 0.1, 0.5, 2.5, 10, 30 mg/kg/d (rats, 20 wk); <ul style="list-style-type: none"> NOAEL: 0.5 mg/kg/d for formation of preneoplastic foci NOAEL (calculated): 1 mg/kg/d for monooxygenase induction Several developmental repeat feeding/gavage studies with rats and rabbits report foetal NOAELs at least 83 times higher than the effective oral dose at the MAK of 0.1 mg/m³. 		



Source	Year set	Standard
Insufficient data to assign a sensitiser notation.		
SCOEL	NA	NA
No report.		
OARS/AIHA	NA	NA
No report.		
HCOTN	2001	TWA 8 hours: 0.5 mg/m³
<p>Summary of additional data:</p> <p>Current administrative OEL considered too high by the agency. Immune system suppression considered most sensitive endpoint based on LOAEL of 0.012 mg/kg/d (24 wk) for this effect in mice (also cited in DFG, 2001), no NOAEL was determined in this study. A health-based recommended OEL (HBROEL) is derived by applying factors of 2 and 10 are applied to respectively account for interspecies differences, and estimation of a NOAEL from the dose-response relationship in the cited study to obtain an HBROEL of 4 µg/m³ assuming 100% absorption in a 70-kg individual with a respiratory volume of 10 m³ over an 8 h shift.</p> <p>A carcinogenicity notation not warranted based on animal studies that show tumour promotion, but lack of tumour initiation capacity.</p> <p>A skin notation is recommended based on reports of dermal absorption in humans (also cited in ACGIH, 2018).</p> <p>Animal data:</p> <ul style="list-style-type: none"> • LC₅₀: 1,600 mg/m³ (rat, 4 h) • Eliminated via urine, faeces, milk, and semen; does not accumulate in significant amounts, half-life from dermal application: 1 d (monkeys), half-life from oral dose 2–4 d (mice, rats) • Immune system suppression at 0.012 mg/kg/d in repeat oral dose study (mice, 24 wk); effects seen at all tested doses 0.012–1.2 mg/kg/d • Liver damage at 60 mg/kg in repeat dermal application study (rats, 6 h, occlusive, 5 d/wk, 13 wk); NOAEL 10 mg/kg • Neurobehavioral changes at 5 mg/kg/d in repeat oral dose study (female rats, 3 mo); NOAEL: 2.5 mg/kg/d • Chronic feeding carcinogenicity studies with mice (also cited in ACGIH, 2018) not considered sufficient evidence for carcinogenic activity in animals; tumour promotion, but not initiation, suggested in feeding study with Lindane and known tumour initiators (rats, 20 wk) • Not considered a genotoxic carcinogen based on weight of evidence of available mutagenicity assays. 		

Secondary source reports relied upon

Source	Year	Additional information
HSE	✓ 1996	<ul style="list-style-type: none"> • 8-h TWA derived from NOAEL of 0.3 mg/m³ for histopathological changes and mortality (mice, 6 h/d, 5 d/wk, 13 wk, also cited by DFG, 2001). Factor of 3 applied to derive a recommended 8-h TWA of 0.1 mg/m³.



Source	Year	Additional information
IARC	✓ 2018	<ul style="list-style-type: none"> Negative or mixed results mutagenicity assays with chromosomal and other DNA damage endpoints in rats, mice, hamsters Negative or small effects reported in bacteria and lower eukaryotes No reliable genotoxicity data available in exposed humans Overall, the mechanistic data provide strong support for the carcinogenicity of lindane including evidence that lindane is immunosuppressive and induces oxidative stress, which can occur in humans Sufficient evidence in humans for the carcinogenicity of lindane Lindane causes non-Hodgkin lymphoma.
US EPA	✓ 1987	<ul style="list-style-type: none"> Gamma-HCH oral reference dose (RfD) calculated principally from 2 feeding studies that reported NOAEL of 0.3 mg/kg/d (rats, 12 wk) 1.6 mg/kg/d (rats, 2 yr) for liver toxicity; carcinogenicity of gamma-HCH not yet assessed Technical grade HCH (t-HCH) assessed as non-genotoxic carcinogen based on liver tumorigenicity in several chronic feeding studies with rodents (also cited in ACGIH, 2018).
US NIOSH	✓ 1994	<ul style="list-style-type: none"> IDLH based on acute oral toxicity data in humans and animals.

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	Skin
HCIS	—
NICNAS	NA
EU Annex	—
ECHA	NA
ACGIH	Carcinogenicity – A3, Skin
DFG	Carcinogenicity – 4, H (skin)
SCOEL	NA
HCOTN	Skin
IARC	Carcinogenicity – Group 1



Source	Notations
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:	yes
Dermal LD ₅₀ ≤ 1000 mg/kg:	yes
Dermal repeat-dose NOAEL ≤ 200 mg/kg:	yes
Dermal LD ₅₀ /Inhalation LD ₅₀ < 10:	yes
<i>In vivo</i> dermal absorption rate > 10%:	
Estimated dermal exposure at WES > 10%:	
a skin notation is warranted	

IDLH

Is there a suitable IDLH value available? Yes

Additional information

Molecular weight:	290.83
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m ³ ; 1 mg/m ³ = Number ppm
This chemical is used as a pesticide:	<input checked="" type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input checked="" type="checkbox"/> DFG <input type="checkbox"/> 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](#) on the ACGIH website.

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

International Agency for Research on Cancer (IARC) (2018) Lindane. IARC Monographs on the evaluation of the carcinogenic risk to humans, volume 113.



Health Council of the Netherlands (HCOTN) (2001) Lindane (γ-hexachlorocyclohexane). Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2001/07OSH.

Tenth Adaptation to Technical Progress Commission Regulation (EU Annex) 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).

UK Health and Safety Executive (HSE) (1996) Lindane (Gamma-HCH) – EH64: Summary criteria for occupational exposure limits.

US Environmental Protection Authority (US EPA) (1987) Integrated Risk Information System (IRIS) Chemical Assessment Summary – gamma-Hexachlorocyclohexane.

US Environmental Protection Authority (US EPA) (1987) Integrated Risk Information System (IRIS) Chemical Assessment Summary – technical Hexachlorocyclohexane (t-HCH).

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – Lindane.