ENDOSULFAN

CAS number:	115-29-7
Synonyms:	Thiodan, 6,7,8,9,10,10-Hexachloro-1,5,5a,6,9,9a-Hexahydro-6,9-methano-2,4,3-benzodioxathiepin 3-oxide, thiodan
Chemical formula:	$C_9H_6Cl_6O_3S$
Structural formula:	—

Workplace exposure standard (retained)

TWA:	**0.1 mg/m³**
STEL:	**—**
Peak limitation:	**—**
Notations:	**Sk.**
IDLH:	**—**

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

Recommendation and basis for workplace exposure standard

A TWA of 0.1 mg/m³ is recommended to protect for lower respiratory tract irritation, liver and kidney damage and central nervous system (CNS) effects in exposed workers.

Discussion and conclusions

Endosulfan has been widely applied as an insecticide (ACGIH, 2009).

The critical effects are respiratory tract irritation, liver and kidney damage, oedema of the brain and lungs and CNS effects. Reliable human exposure data are not available. No effects were seen in rats exposed at 1 mg/m³ for 29 days. A NOEL of approximately 0.5 mg/kg/d was reported from repeated dose studies in rats, mice and dogs. The ACGIH reported this dose as equivalent to a daily inhalation exposure of 3.5 mg/m³ and assigned a TWA of 0.1 mg/m³ (ACGIH, 2018).

The current TWA of 0.1 mg/m³ is recommended to be retained as assigned by the ACGIH (2018) and based on the weight of evidence presented. The recommended TWA is expected to be protective of harmful effects in exposed workers.

Recommendation for notations

Not classified as a 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 as evidence indicates rapid absorption through the skin and reports of acute poisonings in the workplace.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.1 mg/m^3***
ACGIH	***2009***	***TLV-TWA: 0.006 ppm (0.1 mg/m^3)***

TLV-TWA derived from a NOEL of ~0.5 mg/kg/d (based on repeated dose studies in rats, mice and dogs) for protection of lower respiratory tract irritation and liver and kidney damage.

Assuming 100% absorption and inhalation rate of 10 m^3 during an 8 h period, the oral dose corresponds to a daily inhalation exposure of 3.5 mg/m^3; TLV-TWA sufficiently low to protect from unwanted effects (no explanation on TLV-TWA derivation).

Due to fatal effects on animals when applied dermally, a skin notation is assigned.

Summary of data:

Human data:

- 9 workers involved in packaging experienced nausea, vomiting, dizziness and confusion followed by convulsions
- Industrial worker exposed whilst cleaning a vat experienced repeated convulsions and impaired consciousness that led to permanent brain damage
- Several cases of acute poisoning reported death following ingestion of up to 100 mL:
  - initial clinical symptoms included gagging, vomiting, diarrhoea, agitation, unconsciousness, cyanosis, dyspnoea and laboured breathing
  - autopsies revealed oedema of brain and lungs, haemorrhage of the medullary layer of the kidneys, and acute lung emphysema
- Estimated dose of 250 mg/kg dose resulted in severe seizures followed by death of a 43 yr old man within 4 d of exposure. Autopsy revealed pulmonary congestion and atelectasis
- Case-control study did not identify a positive correlation between occupational exposures and incidence of breast cancer. Inconclusive results due to small sample size and co-exposure with other chemicals.

Animal data:

- α-isomer more toxic than the β-isomer in female rodents
- Oral LD_{50}: 8.4 mg/kg (male mice), 10 to 23 mg/kg (female rats more sensitive than males at 40 to 120 mg/kg), 76.7 mg/kg (dogs)
- Dermal LD_{50}: 130 mg/kg (male rats), 78 mg/kg (female rats)
- 4 h LC_{50}: 12.6 mg/m^3 (female rats), 34.5 mg/m^3 (male rats)
- Immediate symptoms following inhalation exposure included irregular respiration:
  - higher concentrations (12.3 mg/m^3 in male rats) resulted in tremors and convulsions, among other CNS complications
- Following exposure (nose-only) to 1 mg/m^3 and 2 mg/m^3 for 6 h/d, 5 d/wk for 21 d, no significant changes were observed in rats:
  - reduced body weight gain noted in male rats at 2 mg/m^3
  - no effects observed at 1 mg/m^3
- Reported NOEL of ~0.5 mg/kg/d from following:
  - no evidence of developmental toxicity observed in pregnant rats dosed at 0.6, 2, or 6 mg/kg from GD 6–19
  - rats orally dosed at 5 mg/kg for 3 days; increased liver weights, RBC and neutrophil counts

Source	Year set	Standard
		○ females rats dosed at 1.5 mg/kg for 30 d demonstrated dyspnoea ○ rats fed 10 mg/kg for 9–18 wk demonstrated hematologic, hepatic and renal damage; no effects at 5 mg/kg ○ no effects other than slight decrease in haemoglobin in rats fed 0.8 and 1.9 mg/kg for 90 d ○ no effects in mice dosed at 2 mg/kg for 13 weeks but cardiac, gastric, hematologic, hepatic renal, endocrine, ocular and congestion in lungs effects were reported at 7.3 mg/kg and 50% of mice died ○ 2-yr study in mice: 60 dose; males 12.5 mg/kg and females 2.9 mg/kg; no increase in neoplastic lesions ○ 2-yr study in rats: males 5 mg/kg/d, females 1.5 mg/kg/d; no increase in neoplastic lesions ○ no effects in dogs feed 2.6 mg/kg for 12 mo; no additional information ○ no effects in rats fed 2.9 mg/kg for 26 wk; no additional information • Several studies concluded no carcinogenic effects on animals following oral exposure • Mixed positive/negative genotoxicity results; increased incidence of chromatid aberrations in mice following exposure to 6.4 mg/kg (for 5 d) but not at 21.7 mg/kg (for 2 d) did not • Developmental effects, including increase in resorptions and skeletal variations, on foetuses of pregnant rats following oral exposure to 5 or 10 mg/kg during GD 6–14. • Available animal studies show no evidence of carcinogenic effects, an A4 notation is recommended.
DFG	***NA***	***NA***
No report.		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source		Year	Additional information
US EPA	✓	1994	• No inhalation RfC • Oral RfD of 0.006 mg/kg/d based on NOAEL: 15 ppm [0.6 mg/kg/d (male); 0.7 mg/kg-d (female)] and LOAEL: 75 ppm [2.9 mg/kg/d (male); 3.8 mg/kg/d (female)] for reduced body weight and increased incidence of marked progressive glomerulonephrosis and blood vessel aneurysms in males (rat, 2 y feeding study).
US NIOSH	✓	2018	• TWA: 0.1 mg/m^3.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	Insufficient data
Is the chemical carcinogenic with a mutagenic mechanism of action?	No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	Skin
HCIS	—
NICNAS	NA
EU Annex	NA
ECHA	—
ACGIH	Carcinogenicity – A4, Skin
DFG	NA
SCOEL	NA
HCOTN	NA
IARC	NA
US NIOSH	—

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	
Conclusion:	
Adverse effects in human case study:	yes
Dermal LD_{50} ≤1000 mg/kg:	yes
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	yes
In vivo dermal absorption rate >10%:	
Estimated dermal exposure at WES >10%:	
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	406.9
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 16.64 mg/m^3; 1 mg/m^3 = 0.06 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
1991	TWA: 0.1 mg/m^3

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.

National Institute for Occupational Safety and Health (NIOSH). (2018). NIOSH Pocket Guide to Chemical Hazards – Endosulfan.

US Environmental Protection Agency (US EPA). (1994). Integrated Risk Information System (IRIS) – Chemical Assessment Summary, Endosulfan; CASRN 115-29-7.