PHENOTHIAZINE

CAS number: 92-84-2

Synonyms: Dibenzothiazine, thiodiphenylamine

Chemical formula: $C_{12}H_9NS$

Workplace exposure standard (retained)

TWA: **5 mg/m^3**

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **—**

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

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Recommendation and basis for workplace exposure standard

A TWA of 5 mg/m^3 is recommended to protect for skin irritation and discolouration, keratitis and photosensitisation in exposed workers.

Discussion and conclusions

Phenothiazine is used as a pesticide, as a base in the manufacture of tranquilisers, as a urinary antiseptic and in the treatment of pinworm, threadworm and roundworm.

Critical effects of exposure include skin irritation and discolouration, keratitis and photosensitisation.

Limited inhalational toxicity data from humans is available, with a report of workers exposed at 15 to 48 mg/m^3 of dust developing hair and fingernail colouration (reversible following cessation of exposure) and skin irritation. Large oral doses in humans caused hepatotoxicity, haemolytic anaemia, abdominal cramps, tachycardia and renal damage (ACGIH, 2018). A sub-chronic feeding study in dogs identified a NOAEL of approximately 5 to 6 mg/kg/day for haemolytic anaemia (DFG, 2009; ECHA, 2006). In the absence of suitable chronic studies, this NOAEL is adjusted to a TWA of 17 mg/m^3 by DFG (2009) but it is noted it may not be protective of phytotoxicity or hair and fingernail discolouration; hence no MAK assigned.

The SWA TWA of 5 mg/m^3 derived by ACGIH (2018) is recommended be retained and is considered sufficiently protective to limit irritant and photosensitisation effects.

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 recommended based on evidence suggesting potential dermal absorption and adverse systemic effects.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 5 mg/m^3***
ACGIH	***2001***	***TLV-TWA: 5 mg/m^3***
TLV-TWA recommended to minimise the potential for skin irritation and discolouration, keratitis and photosensitisation. Summary of data: Human data: • Hepatotoxicity, haemolytic anaemia, abdominal cramps and tachycardia may be caused by large oral doses: o other effects include GI and skin irritation, renal damage, skin photosensitisation and pruritus • Exposed workers during field testing in orchards complained of itching with irritation and reddening of the skin, attributed to absorption through the skin, with some exposure via ingestion or pulmonary absorption possible; concentration not reported • 2 individuals ingesting 3 doses of 0.25 g became photosensitive to UV light • Workers exposed at 15–48 mg/m^3 of the dust developed pinkish-red coloured hair, brown fingernails and skin irritation: o hair and fingernail colouration intensified with increased or prolonged exposure and regressed following cessation of exposure • No other systemic toxicities reported apart from photosensitisation. Animal data: • LD_{50}: 5,000 mg/kg (rats, oral) • Injection into anterior chamber of the eyes of pigs and cattle caused photosensitised keratitis with corneal oedema. A skin notation warranted based on percutaneous absorption reportedly contributing to local and systemic toxicities. Insufficient data to recommend SEN or carcinogenicity notations.		
DFG	***2009***	***Not assigned***
Summary of additional data: • LD_{50}: >10,000 mg/kg bw (rat and rabbit, oral and dermal) • Negative results in several *Salmonella* mutagenicity tests: o mutations induced in mouse lymphoma test in absence of metabolic activation, but not in presence of metabolic activation • Carcinogenicity study in mice (poorly documented) showed no evidence of carcinogenic effects • Due to side effects (including haemolytic anaemia), total therapeutic dose should not exceed 15 g/patient (≈214 mg/kg, assuming 70 kg bw)		

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Source	Year set	Standard
		• No effects on digestive system, circulation, kidneys or liver in 92 patients given oral doses of 3.12–42.9 g (≈45–613 mg/kg, assuming 70 kg bw) (as urinary tract antiseptic) for 3 d–3 mo • NOAEL: ≈5 mg/kg/d (dogs, 13 wk); doses of 0, 1.25, 5, 12.5 and 50 mg/kg/d • Purified or 95% phenothiazine not found to be irritating to rabbit eyes after 24, 48 or 72 h • Based on half the NOAEL of 5 mg/kg/d and 70 kg bw, 10 m^3 breathing volume in 8 h, a concentration of 17 mg/m^3 is calculated as the equivalent inhalational dose. However, effects of discolouration of the fingernails and hair or phytotoxicity may not be protected at this concentration, thus MAK not assigned.
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
ECHA	✓	2006	• NOAEL=6 mg/kg/d (same 13 wk dog study cited by DFG,2009); effect was haemolytic anaemia • Sub-chronic dog study conducted prior to establishment of OECD guidelines, but considered sufficient for assessment.
OECD	✓	2002	• No additional information.
US NIOSH	✓	2007	• REL=TWA 5 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?	Insufficient data

Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	—
HCIS	NA
NICNAS	NA
EU Annex	NA

Source	Notations
ECHA	NA
ACGIH	Skin
DFG	NA
SCOEL	NA
HCOTN	NA
IARC	NA
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:	no
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	
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:	199.26
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:	✓
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* on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2009) Phenothiazin – MAK value documentation.

European Chemicals Agency Regulation (ECHA) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Organisation for Economic Cooperation and Development (OECD) – (2002) SIDS initial assessment profile – 10H Phenothiazine.

US National Institute for Occupational Safety and Health (NIOSH) (2007) NIOSH Pocket Guide To Chemical Hazards, DHHS (NIOSH) Publication No. 2005-149.

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