PARATHION

CAS number: 56-38-2

Synonyms: Bladan, ethyl parathion, O,O-Diethyl O-p-nitrophenyl phosphorothioate, DNTP, paraphos, alkron, alleron, niram

Chemical formula: $C_{10}H_{14}NO_5PS$

Structural formula: —

Workplace exposure standard (interim)

TWA: **0.1 mg/m^3 (inhalable)**

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **10 mg/m^3**

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/m^3 is recommended to protect for cholinergic effects in exposed workers.

Given the limited data available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

Parathion is a broad-spectrum pesticide. However, its use is now banned in Australia. The related methyl parathion (CAS 298-00-0) remains in restricted use.

Critical effects of exposure relate to cholinesterase (ChE) inhibition, measured by red blood cell (RBC) ChE activity; and includes typical cholinergic inhibition symptoms such as headache, nausea, muscular fibrillations and coma (ACGIH, 2018).

Inhalational exposure data for both humans and animals are limited. A NOAEL of 0.05 mg/kg/day for RBC ChE depression was reported in repeat oral dose study (one volunteer), which is consistent with oral dose data obtained from animal feeding studies (ACGIH, 2018). An inhalational equivalent of this NOAEL in humans is 0.35 mg/m^3. However, air concentrations between 0.2 and 0.8 mg/m^3 at the workplace are associated with RBC ChE depression (ACGIH, 2018). Increased incidence of adrenal adenomas and carcinomas is observed in chronically fed rats (ACGIH, 2018); clastogenicity and mutagenicity are evidenced in occupationally exposed workers and human cell cultures, respectively (IARC, 2012).

Noting the insufficient inhalation data and inconsistencies in the primary sources regarding the occupational exposure limits, the TWA of 0.1 mg/m^3 is recommended to be retained. The recommended TWA is expected to minimise the risk for RBC ChE depression and all subsequent

cholinergic symptoms. However, due to the limited data it is recommended that a review of additional sources be conducted at the next scheduled review.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Inconsistencies in carcinogenicity notations exist in the available source material. Parathion is not classifiable as a human carcinogen according to ACGIH (2018) based on the weight of evidence of available chronic animal feeding studies. IARC (2017) evaluated the compound as a possible human carcinogen based on evidence for carcinogenicity in animals in additional studies and evidence for genotoxicity in humans and animals. A review of the available 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 rapid dermal absorption and reports of acute poisonings at the workplace.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.1 mg/m^3***
ACGIH	***2003***	***TLV-TWA: 0.05 mg/m^3 (Inhalable aerosol and vapor)***

TLV-TWA intended to protect for cholinergic effects.

Summary of data:

TLV-TWA derived from NOAEL of 0.05 mg/kg/d and LOAEL of 0.1 mg/kg/d for RBC ChE inhibition reported in volunteer oral dose studies. Conversion of the 0.05 mg/kg/d oral dose to an inhalational equivalent affords 0.35 mg/m^3. Workplace exposures at 0.2–0.8 mg/m^3 were associated with RBC ChE inhibition; TLV-TWA of 0.05 mg/m^3 therefore, considered protective.

Human data:

- Oral and dermal poisoning results in typical cholinergic symptoms progressing from headache, nausea, abdominal pain, miosis, hyperactive bowels and convulsions, to coma:
  - death occurs from respiratory arrest
  - high oral doses cause death in <5 min
- 46% of iv dose (amount not specified) excreted in urine in 120 h, elimination half-life: 8 h
- Dermal doses absorbed 20–30% from emulsion, 0.1–0.2% from absorbent pad, and 10% from acetone solution in volunteer study (300 min)
- Depressed RBC ChE activity in production workers (n=13) at 0.2–0.8 mg/m^3, RBC ChE levels reverted within 5 mo of cessation
- RBC ChE activity reduced to 30–50% of baseline levels in exposed pilots and field workers
- No clinical cholinergic symptoms but ChE inhibition reported in several repeat oral dose studies with volunteers:
  - no decreases in ChE activity at 0.003–0.05 mg/kg/d (males, n=10, 3 d)
  - 50% (plasma) decrease reported at 0.1 mg/kg/d with 15 d (males, n=5, 30 d)
  - 16% (RBC) and 27% (plasma) decrease at 0.1 mg/kg/d (females, 5 d/wk, 6 wk)
- No signs of toxicity, but 70% (RBC) and 71% (plasma) of baseline ChE activity at 0.04 mg/kg/d from inhaled vapour in inhalation study (one volunteer, 0.5 h/d, 4 d).

Animal data:

- Oral LD_{50}: 3–6 mg/kg (female rats), 7–30 mg/kg (male rats), 14–32 mg/kg (mice):
  - comparison of 90-d LD_{50} with single dose LD_{50} indicates no bioaccumulation (rats)
- Dermal LD_{50}: 7 mg/kg (female rats), 21 mg/kg (male rats), 150–2,800 mg/kg (rabbits):
  - *in vivo* dermal penetration rate: 0.33 (males) and 0.49 µg/cm^2/h (females)
- LC_{50}: 32–84 mg/m^3 (rats, 4 h)
- No cholinergic effects but decreased RBC ChE activity above 0.05 mg/kg/d reported in 2 separate sub-chronic feeding studies (rats, 84 d)
- No evidence for carcinogenicity at up to 2.6 mg/kg/d in several chronic feeding studies (rats, mice, dogs, 0.5–2 yr):
  - adrenal adenomas and carcinomas at 2.6 mg/kg/d only in rats in 1 study (mice, rats, 1 yr); regarded as equivocal evidence for carcinogenicity in rats (US NCI) and inadequate evidence to evaluate carcinogenicity (IARC, 1983)

Source	Year set	Standard
• Non-genotoxic in several *in vitro* and *in vivo* studies Insufficient data to recommend a TLV-STEL or sensitiser notation. Not classifiable as human carcinogen (A4) based on negative results in chronic animal carcinogenicity studies. Skin notation recommended based on reports of fatal poisoning from dermal absorption.		
DFG	***1958***	***MAK: 0.1 mg/m³***
Summary of additional data: Exposure durations in available human and animal studies are too short for definitive MAK assessment. Due to lack of evidence for bioaccumulation, MAK of 0.1 mg/m³ expected to be protective of cholinergic effects and is supported by the recommended threshold limit of 0.05–0.1 mg/m³ provided by the WHO; derivation not provided. Skin notation recommended based on rapid dermal absorption. Human data: • Low level of ChE inhibition in production workers exposed at 0.1–0.8 mg/m³, average: 0.2–0.3 mg/m³ (n=12, also cited in ACGIH, 2003) • Air concentrations during crop spraying operations typically between 0.05–0.5 mg/m³. Animal data: • 75–90% of iv dose excreted in urine in 6–24 h (monkeys) • Embryotoxic in rats at acutely toxic maternal doses; available reproductive/developmental studies are inadequate for MAK assessment due to exposure routes and documentation: o increased mortality at 0.63–0.98 mg/kg ip injection (rats, GD 9–15) o mortality and reduced average birth weight at 1.5 and 2.0 mg/kg subcutaneous injection (rats, GD 1, 7, or 13); doses were maternally toxic • No histologically detectable organ damage in chronic feeding studies with rats and dogs (studies also cited in ACGIH, 2003) • NOAEL: 0.4 mg/m³ for RBC ChE inhibition in sub-chronic inhalation study (rats, 6 h/d, 4 mo).		
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
APVMA	✓	2000	• Studies in human volunteers indicate ~10% dose applied to human skin is absorbed, with ~5-fold difference between individuals (no further information)

Source		Year	Additional information
			• Continued use of parathion products would pose an undue hazard to humans.
IARC	✓	2017	• Sufficient evidence for carcinogenicity in animals: o dose-dependent bronchioalveolar adenoma and carcinoma (males) and increased malignant lymphoma (females) at 60–140 ppm of diet reported in chronic feeding study (mice, 18 mo) o no evidence for increased tumour incidence in similar studies with rats • Inadequate evidence for carcinogenicity in humans: o available epidemiological studies are inconclusive due to confounding by mixed exposures or inconsistencies in results o clastogenicity in peripheral lymphocytes in exposed vegetable sprayers (n=25) o DNA damage evidenced in comet assay of human liver HepG2 cells o metabolite, paraoxon, induced DNA strand breaks in human blood lymphocyte cultures o evidence for genotoxicity overall is “moderate”.
US EPA	✓	1988	• Possible human carcinogen based on adrenal adenomas and carcinomas in rats reported in US NCI chronic feeding study (also cited in ACGIH, 2018) • Carcinogenicity supported by positive unscheduled DNA synthesis in human WI-38 cells.
US NIOSH	✓	2015	• *In vitro* penetration rate for human skin: 78.6% • Several cases of poisoning from dermal contact and acute dermal toxicity studies support SK:SYS (Fatal) classification.

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	Skin
HCIS	—
NICNAS	—
EU Annex	—

Source	Notations
ECHA	NA
ACGIH	Carcinogenicity – A4, Skin
DFG	H (skin)
SCOEL	NA
HCOTN	NA
IARC	Carcinogenicity – Group 2B
US NIOSH	SK:SYS (Fatal)

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:	
Dermal LD_{50}/Inhalation LD_{50} <10:	no
In vivo dermal absorption rate >10%:	yes
Estimated dermal exposure at WES >10%:	yes
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available? Yes

Additional information

Molecular weight:	291.27
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.

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Deutsche Forschungsgemeinschaft (DFG) (2002) Parathion – MAK value documentation, German language edition.

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International Agency for Research on Cancer (IARC) Volume 112, Some Organophosphate Insecticides and Herbicides. IARC Monographs.

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).

US Environmental Protection Authority (US EPA) (1988) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Parathion.

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