DIOXATHION

CAS number: 78-34-2

Synonyms: Delnav, 2,3-p-Dioxanedithion S,S-bis-(O,O-diethyl phosphorodithioate), Hercules AC528, Navadel

Chemical formula: $C_{12}H_{26}O_6P_2S_4$

Structural formula: —

Workplace exposure standard (retained)

TWA: **0.2 mg/m^3**

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 0.2 mg/m^3 is recommended to protect for cholinergic effects in the blood and brain, and at higher concentrations, severe neurotoxicity in exposed workers.

Discussion and conclusions

Dioxathion is an organophosphate pesticide and is considered highly toxic. No longer in use, it was previously used to control a variety of pests on crops and livestock.

Critical effects are neurotoxicity by cholinesterase (ChE) inhibition and, at higher concentrations, nausea, weakness, muscular spasms as noted in a case of accidental poisoning in a young boy (ACGIH, 2018).

The current TWA of 0.2 mg/m^3 is recommended to be retained and is consistent with the TWA assigned by HCOTN (2003). The TWA is derived from a NOAEL of 0.075 mg/kg/d for plasma ChE inhibition in a four week continuous repeat oral dose study with volunteers and adjusted to the equivalent inhalational NOAEC of 0.245 mg/m^3 which was rounded down to 0.2 mg/m^3. This value is expected to be protective of more severe neurotoxic effects observed at higher concentrations in animals and accidentally exposed humans (ACGIH, 2018).

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 based on evidence for dermal absorption and adverse systemic effects in animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.2 mg/m^3***
ACGIH	***2002***	***TLV-TWA: 0.1 mg/m^3***

TLV-TWA intended to protect for cholinergic and neurotoxic effects.

Summary of data:

TLV-TWA derived from LOAEL of 0.15 mg/kg/d for cholinesterase inhibition in volunteers of sub-chronic oral dose study. Assuming a 70-kg worker with a respiratory volume of 10 m^3 during an 8-h shift, an air concentration delivering the effective dose at the LOAEL ≡1.0 mg/m^3. Supported by a LOAEL of 0.07 mg/kg/d from a repeat feeding study in dogs (equating to an inhalation dose of 0.5 mg/m^3), the TLV-TWA of 0.1 mg/m^3 is expected protective of cholinergic effects and clinical effects reported at higher doses.

Human data:

- Accidental poisoning of 5-yr old boy at ≈57 mg/kg caused vomiting, diarrhoea, weakness, shallow rapid respiration; recovery within 12 h following treatment
- Slight inhibition of plasma ChE, but no clinical effects at 0.15 mg/kg/d in repeat oral dose study (n=5, 7 d/wk, 4 wk); no RBC ChE inhibition
    - NOAEL of 0.075 mg/kg/d
    - statistically uncertain decrease in plasma ChE activity when 0.075 mg/kg/d co-administered with malathion for last 30 d of additional 60 d study.

Animal data:

- Oral LD_{50}: 23–65 mg/kg (rats); 10-40 mg/kg (dogs)
- LC_{50}: 1,398 mg/m^3 (rats, 1 h); 340 mg/m^3 (mice, 1 h)
- Dermal LD_{50}: 63 and 235 mg/kg (male and female rats, respectively)
- Additive toxicity with other pesticides, 5.4-fold potentiation if given before malathion (rats)
- Diarrhoea, salivation, tremors, ataxia, and RBC ChE inhibition at 8 mg/kg/d in repeat oral dose study (dogs, 14 d); 2.5 mg/kg/d also caused RBC ChE inhibition, >0.8 mg/kg/d affected plasma ChE activity
- Plasma, RBC, and brain ChE inhibition within 1 d at 5 mg/kg/d in repeat oral dose study (rats, 21 d); between d 7 and 21 of study, brain ChE inhibition increased greatly, but little additional effect on RBC and plasma ChE observed
    - similar sub-acute studies with rats had comparable results and showed carboxylesterase activity was affected greater than ChE activity
    - female rats more sensitive than male rats to these effects
- Mild transient conjunctivitis, but no corneal damage with 0.1 mL instilled into rabbit eyes
- Sub-chronic repeat feeding study with treatment groups 0.078, 0.22, 0.78 mg/kg/d (rats, 13 wk) showed RBC and plasma ChE inhibition;
    - NOAEL: 0.22 mg/kg/d for ChE inhibition
    - ChE inhibition observed in RBC and plasma, but not in brain at 0.78 mg/kg/d
    - NOAEL: 0.025 mg/kg/d in comparable study with dogs (5 d/wk, 90 d); LOAEL: 0.07 mg/kg/d for plasma ChE inhibition
- No evidence for carcinogenicity in 78-wk daily feeding study with treatment groups 2.6–5.2 mg/kg (male rats), 1.75–3.5 mg/kg (female rats), 23–47 mg/kg (male mice), 37–74 mg/kg (female mice)
- Extensive 3-gen reproductive repeat feeding study found no abnormalities in any treated animals
- Clastogenic *in vitro* with *Salmonella* and Chinese hamster ovary cells, negative in mouse lymphoma assay.

Source	Year set	Standard
Skin notation recommended due to severe systemic toxicity observed in dermally exposed animals. Not classifiable as a human carcinogen based on chronic feeding studies with mice and rats. Insufficient data to assign a TLV-STEL or sensitiser notation. A BEI is available for the similarly acting terbufos.		
DFG	***NA***	***NA***
No report.		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2003***	***TWA: 0.2 mg/m³***
Summary of additional data: Recommendations for health-based TWA derived from a NOAEL of 0.075 mg/kg/d for plasma ChE inhibition in volunteer study, adjusted for a 5-d work week with a factor of 7/5 (0.105 mg/kg). An overall assessment factor of 3 is applied to account for intraindividual variation to give a NOAEL of 0.035 mg/kg/d. Assuming a 70-kg worker with a respiratory volume of 10 m^3 during an 8-h shift and 100% absorption, an air concentration that would deliver an effective dose at this NOAEL is 0.2 mg/m^3 when rounded down. Skin notation recommended due to dermal/inhalation LD_{50} ratio <10. RBC cholinesterase activity may be used as a surrogate for brain ChE activity for exposure assessments. Animal data: • Dermal absorption ≈20% (cattle) • Nodular hyperplasia observed in male mice of 78-wk repeat feeding carcinogenicity study also presented in ACGIH, 2018 • 75-98% of oral dose excreted within 96 h, 80–87% of which was in urine; most was excreted within 24 h (rats) • Positive in one bacterial *in vitro* mutagenicity test, which is not reflected in available carcinogenicity data with mice and rats.		

Secondary source reports relied upon

Source		Year	Additional information
NTP	✓	1978	• Negative results for long-term carcinogenicity study (also presented in ACGIH, 2018 and HCOTN, 2003)
US NIOSH	✓	2017	• Sufficient animal data to assign acutely fatal skin notation, SK:SYS (FATAL) • No studies available to assess skin sensitising potential

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	Sk.
HCIS	—
NICNAS	NA
EU Annex	—
ECHA	NA
ACGIH	Carcinogenicity – A4, Skin
DFG	NA
SCOEL	NA
HCOTN	Skin
IARC	NA
US NIOSH	SK:SYS

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:	
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%:	yes
Estimated dermal exposure at WES >10%:	
	consider assigning a skin notation

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	456.2
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.

Health Council of the Netherlands (HCOTN) (2003) Dioxathion. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/070.

National Toxicology Program (NTP) (1978) NTP-RoC: Dioxathion 10411-S.

US National Institute for Occupational Safety and Health (NIOSH) (2017) NIOSH Skin Notation Profiles: Dioxathion.