# Dioxathion

| CAS number: | 78-34-2 |
| --- | --- |
| Synonyms: | Delnav, 2,3-p-Dioxanedithion S,S-bis-(O,O-diethyl phosphorodithioate), Hercules AC528, Navadel |
| Chemical formula: | C12H26O6P2S4 |
| Structural formula: | — |

 Workplace exposure standard (retained)

| TWA: | **0.2 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 0.2 mg/m3 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/m3 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/m3 which was rounded down to
0.2 mg/m3. 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/m3 |
|  |
| ACGIH 2002 TLV-TWA: 0.1 mg/m3 |
| 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 m3 during an 8-h shift, an air concentration delivering the effective dose at the LOAEL ≡1.0 mg/m3. 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/m3), the TLV-TWA of 0.1 mg/m3 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 LD50:23–65 mg/kg (rats); 10-40 mg/kg (dogs)
* LC50: 1,398 mg/m3 (rats, 1 h); 340 mg/m3 (mice, 1 h)
* Dermal LD50: 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.

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 m3 during an 8-h shift and 100% absorption, an air concentration that would deliver an effective dose at this NOAEL is 0.2 mg/m3 when rounded down.Skin notation recommended due to dermal/inhalation LD50 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.
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### 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
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### 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  |
| --- |
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|  |  |  |  |
| --- | --- | --- | --- |
| Adverse effects in human case study: |   |   |   |
| Dermal LD50 ≤1000 mg/kg: | yes | 3.00 |   |
| Dermal repeat-dose NOAEL ≤200 mg/kg: |   |   |   |
| Dermal LD50/Inhalation LD50 <10: | yes | 3.00 |   |
| *In vivo* dermal absorption rate >10%: | yes | 3.00 |   |
| Estimated dermal exposure at WES >10%: |   |   |   |
|   |   | 3 | **consider assigning a skin notation** |

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### 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/m3; 1 mg/m3 = 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: | [x]  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*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) 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.