# MONOCROTOPHOS

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|---|---|
| **CAS number:** | 6923-22-4 |
| **Synonyms:** | Azodrin®, dimethyl 2-methylcarbamoyl-1-methylvinyl phosphate, (E)-O,O-dimethyl-O-(1-methyl-3-oxo-1-propenyl) phosphate, Monocron®, Nuvacron® |
| **Chemical formula:** | $C_7H_{14}NO_5P$ |
| **Structural formula:** | — |

### Workplace exposure standard (amended)

| | |
|---|---|
| **TWA:** | **0.05 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 0.05 mg/m$^3$ is recommended to protect for cholinergic effects in exposed workers.

## Discussion and conclusions

Monocrotophos is used as an insecticide.

Critical effects of exposure are cholinesterase inhibition.

Brain cholinesterase inhibition is considered the most sensitive toxic endpoint; red blood cell (RBC) cholinesterase activity is, however, used as a surrogate measure for this endpoint. Sufficient cholinesterase inhibition leads to reversible cholinergic symptoms.

Inhalational exposure data for humans and animals are limited. In humans, NOAEL for RBC cholinesterase inhibition ranged from 0.0057 to 0.015 mg/kg/day in repeat oral dose studies (ACGIH, 2018). This range is consistent with that of NOAEL between 0.005 and 0.0125 mg/kg/day reported for the same endpoints in animals (HCOTN, 2003).

In the absence of suitable inhalational data, the TWA derived by ACGIH (2018) is recommended to be adopted. It is based on the estimated inhalational dose equivalent of the oral NOAEL for RBC cholinesterase inhibition in humans.

## 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 reports of severe cholinergic toxicity following dermal exposure and low ratio of dermal to inhalational toxicity reported in animals (ACGIH, 2018; HCOTN, 2003).

# APPENDIX

## Primary sources with reports

| Source | Year set | Standard |
|---|---|---|
| ***SWA*** | ***1991*** | ***TWA: 0.25 mg/m³*** |
| | | |
| ***ACGIH*** | ***2002*** | ***TLV-TWA: 0.05 mg/m³ (inhalable aerosol and vapour)*** |

TLV-TWA intended to protect for reversible cholinergic effects resulting from cholinesterase inhibition. Not classifiable as a human carcinogen based on lack of carcinogenicity in lifetime animal feeding studies. Skin notation warranted based on reported dermal toxicity in animals.

Summary of data:

Cholinesterase inhibition is the most sensitive toxic endpoint. TLV-TWA derived from NOAEL of 0.015 mg/kg/d for RBC cholinesterase inhibition in volunteer repeat oral dose study, which is supported by NOAEL of 0.03–0.05 mg/kg/d for the same endpoints in animals. The oral NOAEL in humans is converted to an inhalational dose assuming a respiratory volume of 10 $m^3$ over an 8-h shift for a 70-kg worker to arrive at 0.1 $mg/m^3$. Based on the available data, TLV-TWA of 0.05 $mg/m^3$ is considered protective of critical cholinergic effects.

Human data:

- Elimination $t_{1/2}$: 20 h; 67–75% of iv dose excreted in urine within 4–8 h
- Severe cholinergic symptoms, coma and death reported in several cases of accidental acute overexposures *via* dermal contact or ingestion report; acute poisoning may lead to intermediate syndrome, characterised by delayed respiratory distress, weakness and palsies
- Inhalational exposure to ~0.05–0.15 $mg/m^3$ caused no overt symptoms in farmers (n=17); filling spray bottles was associated with plasma cholinesterase inhibition
- 15–24% plasma cholinesterase inhibition at 0.0036–0.0057 mg/kg/d in volunteer repeat oral dose study (1 mo); RBC cholinesterase activity unchanged and no cholinergic effects:
  - associated pilot study reported NOAEL of 0.015 mg/kg/d for RBC cholinesterase inhibition although plasma cholinesterase activity was decreased by 51%.

Animal data:

- Oral $LD_{50}$: 14–20 mg/kg (rats); 63–100 $mg/m^3$ (rats, 4 h)
- Dermal $LD_{50}$: 112–126 mg/kg (rats); 270–354 mg/kg (rabbits):
  - no cholinergic symptoms at dose range 20–40 mg/kg/d (rabbits, repeat dermal, 6 h/d, 5 d/wk, 3 wk)
- Sub-chronic feeding study dose range 0.01–0.6 mg/kg/d (rats, 8–13 wk) reported:
  - NOAEL: 0.01 mg/kg/d for brain cholinesterase inhibition
  - 95% brain cholinesterase activity at 0.01 mg/kg/d
  - 0.6 mg/kg/d caused significant RBC (15%), plasma (35%) and brain (27%) cholinesterase inhibition
  - similar toxicity reported in 90 d repeat gavage study, treatment range 0.3–1.2 mg/kg/d
- Dose-dependent liver degeneration and inflammation reported in sub-chronic feeding study, dose range: 0.4–1.5 mg/kg/d (mice, 6 wk):
  - no evidence for liver toxicity or carcinogenic activity in chronic feeding study at 0.15–1.5 mg/kg/d; dose-related cholinesterase inhibition reported at all tested levels
- No gross histopathology or carcinogenicity in 2 chronic feeding studies (rats, 2 yr):

| Source | Year set | Standard |
|---|---|---|
| | | o NOAEL: 0.002–0.05 mg/kg/d for RBC, plasma and brain cholinesterase inhibition<br>• Minimal changes to cholinesterase activity at 0.04 mg/kg/d considered NOAEL in chronic feeding study (dogs, 2 yr); LOAEL: 0.4 mg/kg/d<br>• Mutagenic *in vitro* in bacteria and *in vivo* in *Drosophila melanogaster* and chickens but negative *in vivo* in a dominant lethal cell assay with mice.<br><br>Insufficient data available for recommendation of SEN notation or a TLV-STEL. |
| ***DFG*** | ***NA*** | ***NA*** |
| No report. | | |
| ***SCOEL*** | ***NA*** | ***NA*** |
| No report. | | |
| ***OARS/AIHA*** | ***NA*** | ***NA*** |
| No report. | | |
| ***HCOTN*** | ***2003*** | ***TWA: 0.25 mg/m³*** |
| Summary of additional data:<br>Current administrative level considered unprotective of critical effects. Brain cholinesterase inhibition considered most sensitive endpoint; RBC cholinesterase inhibition used as surrogate measurement and is expected to be equally sensitive based on animal studies. Health-based recommendation (HBROEL) derived from NOAEL of 0.006 mg/kg/d for RBC cholinesterase inhibition in volunteers. A factor of 7/5 is applied to account for continuous exposure under experimental conditions followed by an assessment factor of 3 to account for intraindividual variation to arrive at a NAEL of 0.003 mg/kg/d. This NAEL is converted to an inhalational dose assuming a respiratory volume of 10 $m^3$ over an 8-h shift in a 70 kg worker to obtain the proposed HBROEL of 0.02 $mg/m^3$ as an 8-h TWA.<br>A skin notation is warranted based on reports of systemic effects resulting from dermal absorption.<br>Human data:<br>• Dermal absorption rate of 4 µg/$cm^2$ dermal dose was 7.3 ng/$cm^2$/h (n=6, 24–48 h)<br>• NOAEL >0.0057 mg/kg/d for RBC cholinesterase inhibition in volunteer repeat oral dose study (also cited in ACGIH, 2018); recovery of plasma cholinesterase activity is slower in humans than in animals.<br>Animal data:<br>• No evidence for bioaccumulation following oral dose (rats)<br>• Several sub-chronic oral dose studies with various species report NOAEL range of 0.005–0.125 mg/kg/d (5–13 wk) for cholinesterase inhibition:<br>o agency considers NOAEL of 0.0125 mg/kg/d for RBC and brain cholinesterase inhibition the most biologically relevant (rats, 8–13 wk, also cited in ACGIH, 2018)<br>• Positive mutagenicity consistent with weak DNA alkylating ability; positive results in comet assay with mouse leukocytes and negative results in other *in vivo* studies suggests DNA damage is repairable and therefore not reflected in chronic carcinogenicity studies. | | |

## Secondary source reports relied upon

NIL.

## Carcinogenicity — non-threshold based genotoxic carcinogens

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|---|---|
| Is the chemical mutagenic? | Yes |
| 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 | — |
| HCIS | — |
| NICNAS | NA |
| EU Annex | — |
| ECHA | — |
| ACGIH | Carcinogenicity – A4, Skin |
| DFG | NA |
| SCOEL | NA |
| HCOTN | Skin |
| 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: | yes | |
| Dermal repeat-dose NOAEL ≤200 mg/kg: | yes | |
| Dermal $LD_{50}$/Inhalation $LD_{50}$ <10: | no | |
| *In vivo* dermal absorption rate >10%: | no | |
| Estimated dermal exposure at WES >10%: | yes | |
| | | **a skin notation is warranted** |

## IDLH

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| Is there a suitable IDLH value available? | No |

## Additional information

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| Molecular weight: | 223.2 |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = 9.13 mg/m$^3$; 1 mg/m$^3$ = 0.11 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.

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).

Health Council of the Netherlands (HCOTN) (2003) Monocrotophos. Health-based reassessment of administrative occupational exposure limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/073.

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).