ROTENONE (COMMERCIAL)

CAS number: 83-79-4

Synonyms: Cube ENT 133, 5-beta-rotenone, 1,2,12a-trahydro-8,9-dimethoxy-2-(1-methylethynyl)-[1]benzopyranol-[3,4-b]furo[2,3-h][1]benzopyran-6(6H)-one

Chemical formula: $C_{23}H_{22}O_6$

Structural formula: —

Workplace exposure standard (interim)

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

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **2,500 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 5 mg/m^3 is recommended to protect for potential adverse systemic and developmental 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

Rotenone is used as a pesticide.

Critical effects of exposure are irritation of the mucous membranes and skin, dermatitis, rhinitis and transient loss of olfaction (smell). At higher concentrations, liver damage, breathing difficulties, tremors and coma may occur.

There are no quantitative human exposure data available, a threshold for irritation is not reported in the available exposure data. In chronically exposed rats, a NOAEL of 0.2 mg/kg/day for (unspecified) tissue damage is reported (ACGIH, 2018) and equivocal evidence for carcinogenicity is reported above a NOAEL of 1.7 mg/kg/day (ACGIH, 2018; DFG, 2003). A NOAEL of 0.38 mg/kg/day is reported in a developmental multigenerational feeding study in rats (US EPA, 1988). An acute dermal dose of 100 to 200 mg/kg is lethal to rabbits (DFG, 2003).

A threshold for mucous membrane and skin irritation cannot be determined from the available toxicological data. The TWA of 5 mg/m^3 by SWA and ACGIH (2018) is recommended to be retained in the interim based on an absence of complaints in the workplace at this concentration and a NOAEL of 0.2 mg/kg/day for systemic effects in rats (ACGIH, 2018). This value is also expected to be protective of potential developmental toxicity observed in rats above 0.38 mg/kg/day (US EPA, 1988). However,

further assessment of additional sources, specifically regarding quantitative data on irritation effects and skin absorption, is recommended during subsequent reviews.

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 due to evidence of dermal absorption and contribution to 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 intended to protect for irritation of the mucous membranes and skin, dermatitis, rhinitis, transient loss of olfaction. At higher concentrations, vomiting, drowsiness, abdominal pain, muscle tremors, incoordination, depressed respiration and coma.

Not classifiable as a human carcinogen (A4) based on negative or equivocal evidence for carcinogenicity in animals. TLV-TWA presumably based on recommendation of a cited article that a daily dose of 7 mg/d ≡5 mg/m^3 should not be exceeded in occupationally exposed workers based on systemic effects reported in rats above 0.2 mg/kg/d.

Summary of information:

No adverse effects in exposed workers at 5 mg/m^3 since TLV-TWA establishment in 1957. Exposure at TLV-TWA is equivalent to an oral dose of 0.7 mg/kg/d and considered sufficiently low to be protective of systemic effects. ACGIH notes that a lower OEL, based on particle size, derivation is discussed.

Human data:

- Estimated lethal dose from accidental poisoning 40 mg/kg:
  - symptoms were drowsiness, vomiting, depressed respiration, apnoea and coma
- Dermatitis near genitals, ulcerative rhinitis with anosmia and skin and mucous membrane irritation reported in workers exposed to powder (no details on exposure provided).

Animal data:

- Toxicity depends on particle size; suspensions less toxic than solutions:
  - mechanism of toxicity due to inhibition mitochondrial respiration at the site of interaction
- Oral LD_{50}: 25–132 mg/kg (rats), 1,500 mg/kg (rabbits), 13–130 mg/kg (guinea pigs)
- Fatty liver and kidney degeneration at 5 mg/kg/d in repeat feeding study (dogs, 1 mo):
  - 10 mg/kg/d lethal
- Bone marrow atrophy, reduced bodyweight gain and inflammation of the forestomach at 150/300 ppm of diet (female/male) in subchronic feeding study with exposure groups 0, 75, 150, 300, 600, and 1,200 (rats, 13 wk); increased mortality at 600 ppm of diet:
  - similar study with exposure groups 0, 600, 1,900, 5,000, 16,000, and 50,000 ppm of diet (mice, 13 wk); increased mortality at 16,000 ppm of diet
- NOAEL: 2 ppm of diet (0.2 mg/kg/d) for tissue damage (not specified) in chronic feeding study (rats, 2 yr):
  - LOAEL: 5 ppm of diet (0.5 mg/kg/d), cited article recommends daily occupational exposure should not exceed 7 mg/d
- Reduced body weight gain at 2.5 ppm of drinking water in chronic feeding study (rats, 2 yr)
- Equivocal evidence for carcinogenic activity (parathyroid adenomas) in males, but none in females, at 3.5 mg/kg/d in controlled lifetime feeding study (rats, 2 yr):
  - NOAEL: 1.7 mg/kg/d:
  - no evidence for carcinogenic activity in parallel study at 115 and 250 mg/kg/d (mice, 2 yr)

Source	Year set	Standard
• NOAEL: 2.5 mg/kg/d for foetal and maternal toxicity (reduced maternal body weight gain, foetal weight and ossification, and increased incidence of extra ribs) in oral dose study (rats, GD 6–15): o LOAEL: 5 mg/kg/d, maternal mortality (60%) at 10 mg/kg/d • Non-genotoxic *in vitro* in bacteria and mammalian cell lines; evidence for DNA damage in leukaemia cells likely due to ATP depletion and subsequent inhibition of DNA repair. Insufficient data to recommend a TLV-STEL, or notations for skin absorption, or sensitisation.		
DFG	***2000***	***Not assigned***
Summary of additional information: Previous MAK of 5 mg/m^3 withdrawn due to insufficient data regarding irritation threshold in animals and humans; previous MAK based on systemic effects observed in animal feeding studies. Not considered carcinogenic based on available chronic carcinogenicity studies with animals and negative mutagenicity. Skin notation warranted due to low dermal LD_{50} in rabbits. Human data: • Mild transient rash in 1 volunteer and mild stinging sensation in another when applied as powder (no further details) to armpits in volunteer study (n=4, 2 times/d, 30 d). Animal data: • LD_{50}: 100–200 mg/kg (rabbits, dermal) • Delayed body weight gain and increased relative liver weight at 30 mg/kg/d in subchronic feeding study with exposure group 7.5, 15, 30, 60, and 120 mg/kg/d (rats, 13 wk, also cited by ACGIH, 2018): o NOAEL: 7.5 mg/kg/d: o no NOAEL determined in similar 13 wk feeding study with mice (also cited by ACGIH, 2018), exposure groups 90, 285, 750, 2,400, 7,500 mg/kg/d; relative liver weights increased at 90 mg/kg/d, no pathological or clinical effects noted) • Equivocal evidence for carcinogenicity observed in chronically fed rats above a NOAEL of 1.7 mg/kg/d (rats, 2 yr, also cited by ACGIH, 2018) considered non-significant with respect to historical incidences of parathyroid adenomas in controls • Slightly irritating to rabbit skin (no further details provided) • Does not interact with DNA, not considered mutagenic based on negative results of available *in vitro* studies with bacterial and mammalian cells • Maternal toxicity (no further details), but no spontaneous abortions or resorptions at 40 mg/kg/d in developmental feeding study with exposure groups 1, 10, 20, 40, 60, 80 mg/kg/d (rats, GD 6–15). Insufficient data to recommend a sensitiser notation.		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		

Source	Year set	Standard
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✗	2018	• Tier I: agricultural and therapeutic use not assessed.
US EPA	✓	1988	• Reduced offspring weight at 1.88 mg/kg/d and reduced litter sizes at 3.8 mg/kg/d in 2 generation chronic feeding study with dose groups 0, 0.38, 1.88, and 3.8 mg/kg/d (rats, F_0: 105 d, F_1: 120 d); NOAEL: 0.38 mg/kg/d: o used principally to derive oral RfD • Inhalational RfD and carcinogenic activity not assessed.
US NIOSH	✓	1994	• IDLH based on acute oral toxicity data in humans.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	—
HCIS	—
NICNAS	NA
EU Annex	—
ECHA	—
ACGIH	Carcinogenicity – A4
DFG	H(skin)
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:	yes	
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?	Yes

Additional information

Molecular weight:	394.4
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) (2003) Rotenone – MAK value documentation.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2018) [1]Benzopyrano[3,4-b]furo[2,3-h][1]benzopyran-6(6aH)-one,1,2,12,12a-tetrahydro-8,9-dimethoxy-2(1-methylethenyl)-,[2R-(2.alpha.,12alpha.)]: Human health tier I assessment – IMAP report.

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

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