



PYRETHRUM

CAS number: 8003-34-7

Synonyms: Pyrethrin, Cinerin, Jasmolin

Chemical formula: $C_{21}H_{28}O_3$ or $C_{22}H_{28}O_5$

Structural formula: —

Workplace exposure standard (amended)

TWA: 1 mg/m³

STEL: —

Peak limitation: —

Notations: Sk.

IDLH: 5,000 mg/m³

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 1 mg/m³ is recommended to protect for irritation, liver damage and potential sensitisation in exposed workers.

Discussion and conclusions

Pyrethrum is a botanical extract containing pyrethrins, which are used as insecticides.

Critical effects of exposure are respiratory tract irritation and liver and respiratory tract damage.

Quantitative human inhalational data are limited. In sub-chronically exposed rats, a LOAEC of 11 mg/m³ for respiratory tract damage (DFG, 2008) and a NOAEC of 38 mg/m³ for breathing difficulties, lachrymation and anaemia (HCOTN, 2004) are reported.

Irritation is considered a more sensitive endpoint than systemic endpoints as evidenced in chronic and sub-chronic exposure studies with animals (DFG, 2008). In the absence of reliable human inhalational exposure data and uncertainty in the composition of pyrethrum extracts, the previous TWA of 5 mg/m³ is potentially unprotective as it is too close to the LOAEC of 11 mg/m³ for irritation in rats.

The OEL (HBROEL) of 1 mg/m³ by HCOTN (2004) and TWA by SCOEL (2003) is recommended be adopted. The recommended TWA of 1 mg/m³ is expected to be sufficiently low to protect for both irritation and systemic endpoints and is supported by the health-based recommended.

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. Several cases of dermal sensitisation in patients with dermatitis are reported (ACGIH, 2018; DFG, 2008). However, purified pyrethrins are non-sensitising in animals and positive responses are likely due to the presence of sensitising impurities (HCOTN, 2004; SCOEL, 2003). Due to this conflicting information, a review of the classification is recommended.

A skin notation is recommended as evidence indicates contact dermatitis in humans.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 5 mg/m ³

Source	Year set	Standard
ACGIH	2001	TLV-TWA: 5 mg/m³
TLV-TWA intended to protect for liver and respiratory damage and minimise potential for sensitisation; may not prevent development of sensitisation in individuals susceptible to pollen allergies. Not classifiable as a human carcinogen (A4) based on chronic animal studies. Summary of information: Based on available human and animal exposure data, TLV-TWA of 5 mg/m³ considered sufficiently low to be protective of liver damage and respiratory irritation observed in animals (derivation not presented). ACGIH states level of protection regarding sensitisation in predisposed individuals is uncertain. Human data: - Repeated exposures over 2–3 yr caused development of allergies: dermatitis, localised oedema in face, rhinitis, tachycardia and sweating 1 case of pulmonary interstitial fibrosis from pyrethrum hypersensitivity - Susceptibility to dermatitis increased in hot weather, UV radiation and heavy perspiration 1 case of allergic dermatitis from exposure to powder confirmed with patch test (no details on exposure available) - Except for 1 compound (pyrethrin II), refined pyrethrins were inactive in patch test study (no further details provided) - Response to pyrethrum in 6/200 patients evaluated for dermatitis; 40% of patients allergic to ragweed pollen sensitive to pyrethrins - Cited study estimates occupational exposure at air concentration of 5 mg/m³ $\equiv$ oral dose of 0.7 mg/kg/d. Animal data: - LD₅₀: 273–796 mg/kg (rats, oral) for range of pyrethrins effects: excitation, tremors and shock - Lung congestion at 6,000 mg/m³ (rats, 0.5 h) - No signs of systemic toxicity at 1,500 mg/kg applied dermally (rats) - Slight lung irritation at 16 mg/m³ (rats, dogs, 0.5 h/d, 31 d) - Dyspnoea, tremors, ataxia and salivation at 5,000 ppm in subchronic feeding study (dogs, 90 d) - NOAEL: 50 mg/kg/d for tissue damage (not specified) reported in 1 chronic feeding study (rats, 2 yr): - another study reported liver lesions and focal necrosis at 50 and 250 mg/kg/d (rats, 2 yr, no further details) - No reproductive toxicity at 250 mg/kg/d (rats, 3 wk): - no developmental toxicity at 90 mg/kg/d (rats, GD 8–16) 53% of oral dose exhaled as CO₂; 7% excreted in urine (duration not specified). Insufficient data to recommend a TLV-STEL or notations for skin absorption or sensitisation.		

Source	Year set	Standard
DFG	1997	Not assigned
Summary of additional information: Irritation considered more sensitive than systemic endpoints; NOAEL for liver damage 4 mg/kg/d in female rats in chronic feeding study, $\approx$air concentration of 28 mg/m³ in occupationally exposed humans. Irritation reported at LOAEL of 11 mg/m³ in sub-chronically exposed rats, previous MAK of 5 mg/m³ withdrawn due to insufficient data to derive NOAEC for irritation. Slight increase in liver tumour incidence compared to controls in chronic feeding study in rats insufficient to warrant carcinogenicity classification. Skin notation not warranted based on studies with dermally exposed humans and monkeys. Dermal sensitiser notation recommended based on reports of dermatitis in humans, which are supported by positive results in an inadequately conducted animal study. Human data: • 40–81% of oral dose of 0.3 mg eliminated within 30 h (n=3) • 0.4% of dermal dose detected in urine after 2 d • Slight pulmonary lesions resulting from respiratory irritation in group of workers (n=18, 11–22 yr) exposed at 78 ppm (1,050 mg/m³) of pyrethrin extract (purity not specified) or 6,000 ppm of pyrethrum powder (no further details): ◦ separate lower exposure group (n=59) showed no effects on haematological parameters, electrolyte concentrations and blood biochemistry (no further details) • Positive reactions in 1–2% of patients with dermatitis in clinical patch test studies (n=1,406 and 1,835). Animal data: • LC₅₀: 3,400 mg/m³ (rats, 4 h, inhalation) • Histological changes to larynx (squamous metaplasia) at 11 mg/m³ in subchronic inhalation study with dose groups 0, 11, 30, 100, 356 mg/m³ (rats, 6 h/d, 5 d/wk, 13 wk); nasal discharge and anaemia at 30 mg/m³, mortality at 356 mg/m³: ◦ not possible to calculate NOAEC due to high incidence of larynx lesions at LOAEC • Increased incidence of thyroid adenomas and liver weights at 43/56 mg/kg/d (male/female), hepatocellular adenomas at 130/170 mg/kg/d in chronic feeding study with dose groups 0, 4/5, 43/56, 130/170 mg/kg/d (rats, 2 yr): ◦ NOAEL: 4/5 mg/kg/d ◦ increased incidence of liver and thyroid tumours considered, by the agency, due to induction of liver enzymes and subsequent tumour promotion effect • Dermal absorption rate of 1.9% <i>in vivo</i> (monkeys) • Non-mutagenic <i>in vitro</i> in bacteria or rat hepatocytes; no <i>in vivo</i> mutagenicity data for purified extracts available: ◦ clastogenicity reported at 22.5–90 mg/kg (60% pyrethrins) not considered in evaluation due to use of crude extract (mice, 1–5 doses). Insufficient data to assign a respiratory sensitiser notation.		
SCOEL	2003	TWA: 1 mg/m³
Summary of additional information: Recommended TWA based on NOAEL of 10 mg/kg/d for slight liver damage in chronic feeding study with rats. An overall UF of 50 is applied to account for uncertainty in the chemical composition of commercial extracts, chronic effects in humans and toxicity of oral versus parenteral administration to estimate a NOAEL in humans of 0.2 mg/kg/d. An air concentration that would		

Source	Year set	Standard
deliver an effective dose at this NOAEL is 1 mg/m³ assuming a respiratory volume of 10 m³ in a 70 kg worker during an 8 h shift. Human data: - No additional information presented. Animal data: - LD₅₀: 1,100–3,680 mg/kg (rabbits, dermal) - Pyrethrin I and II aerosols non-sensitising to guinea pigs; suggests positive sensitisation to pyrethrum extracts caused by impurities, e.g. sesquiterpene lactones, present in unrefined formulations - NOAEL: 10 mg/kg/d for slight liver damage in chronic feeding study (rats, 2 yr, also cited in ACGIH, 2018, but NOAEL not reported).		
OARS/AIHA	NA	NA
No report.		
HCOTN	2004	TWA: 5 mg/m³
Summary of additional information: Current administrative OEL considered too high. HBROEL derived from NOAEC of 38 mg/m³ for systemic effects in subchronically exposed rats. UF of 27 applied to this NOAEC accounting for intra- and interspecies differences and translation from experimental conditions to the workplace; rounding down arrives at the proposed HBROEL of 1 mg/m³. The HBROEL is expected to be sufficiently low to protect for both respiratory tract irritation and systemic effects observed in rats. Skin notation not warranted due to low dermal penetration in humans and animals. Human data: - Cases of allergic dermatitis and asthma considered to be caused by impurities, which are no longer present in purified products. Animal data: - NOAEL: 20/40 mg/kg/d (females/males) based on neurological disorders and behavioural abnormalities in an unpublished gavage study; dose groups 0, 20/40, 63/125, 200/400 mg/kg/d (females/males, rats, 13 wk); mortality at 200/400 mg/kg/d - NOAEC: 38 mg/m³ for laboured breathing, tremor, lachrymation, haematological changes (anaemia) and decreased body weight gain reported in sub-chronic inhalation study with dose groups 0, 38, 68, 230, 830 mg/m³ (rats, 6 h/d, 5 d/wk, 13 wk): - lesions in the larynx observed in all groups, including controls, more pronounced in the pyrethrin-exposed groups - HCOTN considers NOAEC of the study for systemic effects, not necessarily local irritation effects - No signs of toxicity at 1,000 mg/kg/d in repeat dermal application study (rabbits, 21 d) - Carcinogenicity observed in rats and mice (also cited in DFG, 2008) not considered to be caused by genotoxic mechanism. - Non-mutagenic <i>in vitro</i> with or without metabolic activation in bacteria and mammalian cells; no suitable <i>in vivo</i> data available for evaluation.		

Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✱ 2018	• Tier I: agricultural and therapeutic use 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	Sen
HCIS	—
NICNAS	—
EU Annex	—
ECHA	—
ACGIH	Carcinogenicity – A4
DFG	Sh (dermal sensitiser)
SCOEL	—
HCOTN	—
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:	no
Dermal repeat-dose NOAEL ≤ 200 mg/kg:	
Dermal LD ₅₀ /Inhalation LD ₅₀ < 10:	
<i>In vivo</i> dermal absorption rate > 10%:	no
Estimated dermal exposure at WES > 10%:	
a skin notation is warranted	

IDLH

Is there a suitable IDLH value available?

Yes

Additional information

Molecular weight:	328.4
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) (2008) Pyrethrum – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2003) Recommendation from the Scientific Committee on Occupational Exposure Limits for pyrethrum. SCOEL/SUM/95.

Health Council of the Netherlands (HCOTN) (2004) Pyrethrum (pyrethrins). Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/138.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2018) Pyrethrins and Pyrethroids: Human health tier I assessment – IMAP report.

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