

ISOPHORONE

CAS number: 78-59-1

Synonyms: Isoacetophorone, isoforon, α -isophorone, 3,5,5-trimethyl-2-cyclohexen-1-one

Chemical formula: $C_9H_{14}O$

Structural formula: —

Workplace exposure standard (retained)

TWA: —

STEL: —

Peak limitation: 5 ppm (28 mg/m³)

Notations: Carc. 2

IDLH: 200 ppm

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

Recommendation and basis for workplace exposure standard

A peak limitation of 5 ppm (28 mg/m³) is recommended to protect for acute eye and upper respiratory tract irritation, nausea and fatigue in exposed workers.

Discussion and conclusions

Isophorone is used as a solvent and intermediate in pesticide production.

Critical effects of exposure are eye, nose and throat irritation and at higher concentrations, nausea, malaise and fatigue. Workplace concentrations between 5 and 8 ppm have been associated with complaints of nasal irritation and pre-narcotic symptoms such as malaise and fatigue. These results are consistent with those reported in volunteer acute inhalation studies (ACGIH, 2018, Nordic Council, 1991). The severity of symptoms increases rapidly with increased concentration with the maximal tolerable exposure in humans over eight hours reported as 10 ppm. This concentration is also associated with reports of fatigue. At 25 ppm, immediate local irritation is reported (ACGIH, 2018).

In view of the sensitivity of irritation and pre-narcotic endpoints and the suggested steep dose-response curve, it is recommended that the peak limitation of 5 ppm (28 mg/m³) be retained. A peak limitation is expected to protect for adverse effects in exposed workers.

Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Renal carcinogenicity is demonstrated in male rats, which warrants a category 2 carcinogenicity notation. However, this effect is attributed to species-specific metabolism that has questionable relevance to human exposure (ACGIH, 2018; OECD, 2003).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

There are insufficient data to recommend a skin notation.

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APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	Peak limitation: 5 ppm (28 mg/m³)
ACGIH	2001	TLV-Ceiling: 5 ppm (28 mg/m³)
<p>TLV-Ceiling intended to protect for irritation of the eyes, nose and throat, nausea, malaise and fatigue.</p> <p>Assigned as a confirmed animal carcinogen with unknown relevance to humans.</p> <p>Summary of data:</p> <p>TLV-Ceiling based on 5–8 ppm associated with fatigue and malaise and no complaints at 1–4 ppm.</p> <p>Equivocal evidence for carcinogenicity reported in rats disregarded by agency due to established rat-specific metabolism that results in nephropathy.</p> <p>Genotoxicity studies do not indicate a genotoxic mechanism of action for the observed carcinogenicity in rats.</p> <p>Human data:</p> <ul style="list-style-type: none"> • Eye nose and throat irritation at 40–400 ppm: <ul style="list-style-type: none"> ○ nausea, headache, dizziness, inebriation and sensation of suffocation at 200 and 400 ppm (no further details provided) • Irritating to eyes, nose and throat at 25 ppm in unconditioned volunteers (15 min): <ul style="list-style-type: none"> ○ highest tolerable level for 8 h was 10 ppm ○ inadequate for preventing fatigue ○ 1–4 ppm did not receive complaints (no further details provided). <p>Animal data:</p> <ul style="list-style-type: none"> • LC_{LO}: 885 ppm (rats, 8 h); mucosal irritation, pulmonary inflammation and CNS depression reported, death occurs from narcosis • Oral LD₅₀: 2,100–2,700 mg/kg (rats); GIT inflammations and congestion of lungs, adrenals, pancreas and kidneys • LD₅₀: 1,390 mg/kg (rabbits, 24 h, dermal) • Eye and skin irritation in sub-chronic inhalation study at 500 ppm (rats, n=10/sex, 8 h/d, 5 d/wk, 4–6 mo); only one concentration tested, three deaths occurred • Dose-dependent mortality and reduced growth in sub-chronic inhalation study with impure substance, treatment range: 25–500 ppm (rats, guinea pigs, 8 h/d, 5 d/wk, 6 wk): <ul style="list-style-type: none"> ○ mortality increased at 100 ppm; severe injury to lungs and kidneys in necropsy ○ non-dose-dependent incidence of liver, lung and kidney congestion in survivors • Systemic irritant as shown by no change in leukocyte count following adrenalectomy and exposure at 67–90 ppm (rats): <ul style="list-style-type: none"> ○ reduction in leukocytes observed at these concentrations prior to adrenalectomy • Eye and nose irritation at 250 ppm in chronic inhalation study (rats, 8 h/d, 5 d/wk, 18 mo) • Dose-dependent increase in renal tumours and nephropathy at 250 and 500 mg/kg/d in chronic gavage studies (rats, mice, n=50/sex, 5 d/wk, 2 yr): <ul style="list-style-type: none"> ○ increased mineralisation in male rats, but decreased in females • No evidence of adverse reproductive or developmental effects at 500 ppm in repeat inhalation study (rats, 6 h/d, 5 d/wk, 3 mo) 		



Source	Year set	Standard
<ul style="list-style-type: none"> No evidence for teratogenicity in repeat inhalation study treatment range 25–115 ppm (rats, 6 h/d, gestation d 6–15); 115 ppm caused reduced maternal bw and food intake Non-mutagenic <i>in vitro</i> and <i>in vivo</i> Inhalational dose distributed to kidneys, adrenals, liver, pancreas and brain. <p>Insufficient data to recommend a TLV-STEL or notations for skin absorption and sensitisation.</p>		
DFG	2014	MAK: 2 ppm (11 mg/m³)
<p>Only a 2014 substance review document and 1977 MAK documentation were retrievable during the current evaluation.</p> <p>Summary of additional data (from 1977 MAK documentation):</p> <p>Human data:</p> <ul style="list-style-type: none"> Volunteer inhalation study (n=96, 5 min) reported: <ul style="list-style-type: none"> malaise and 40% odour perception at 10 ppm irritating to eyes, nose and throat and 70% odour perception at 25 ppm pre-narcotic symptoms at 40–85 ppm severe eye and respiratory tract irritation at 400 ppm corneal damage was transient (no further details provided) No exposure-related complaints at workplace air concentrations of 1–4 ppm: <ul style="list-style-type: none"> fatigue and discomfort at 5–8 ppm after 1 mo. <p>Animal data:</p> <ul style="list-style-type: none"> Substance is narcotic, damages kidneys upon cumulative intake, absorbed rapidly in the lungs and excreted in urine following metabolic oxidation Sub-chronic inhalation study (also cited in ACGIH, 2018) reported NOAEC of 25 ppm for histopathological changes in kidneys and liver (rats, guinea pigs, 8 h/d, 5 d/wk, 6 wk). 		
SCOEL	NA	NA
No report.		
OARS/AIHA	NA	NA
No report.		
HCOTN	NA	NA
No report.		

Secondary source reports relied upon

Source	Year	Additional information
HSE	✓ 2002	<ul style="list-style-type: none"> 15 min STEL: 5 ppm (29 mg/m³)



Source	Year	Additional information
NICNAS	✓ 2013	<ul style="list-style-type: none"> • Eye irritation in volunteers at 25 ppm (n=12, 15 min) • LC₅₀: 1,240 ppm (rats, duration not specified) • Non-irritating to rabbit skin (4 h, semi-occlusive patch) • Non-sensitising in standardised maximisation test (guinea pigs, no further information provided) • Transient nasal bleeding, changed haematological parameters and bw decrease at 44 ppm in sub-chronic inhalation study (rats, 6 h/d, 5 d/wk, 4 wk) • Not expected to be genotoxic based on weight of evidence.
Nordic Council	✓ 1991	<ul style="list-style-type: none"> • Critical effect is mucous membrane irritation • 15 min exposures at 8 ppm cause nasal irritation • Unlikely to have genotoxic potential.
OECD	✓ 2003	<ul style="list-style-type: none"> • Positive result in 1 mouse lymphoma assay, but majority of <i>in vitro</i> and <i>in vivo</i> genotoxicity 'clearly negative'; therefore, not considered mutagenic • Kidney tumours observed in chronic gavage study with rats (also cited by ACGIH, 2018) are attributed to male rat-specific α2u-globulin associated mechanism; observed nephropathy is therefore irrelevant to other species.
US NIOSH	✓ 1994	<ul style="list-style-type: none"> • IDLH based on acute inhalation toxicity data in humans and animals.

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	Carc. 2
HCIS	Carcinogenicity – category 2
NICNAS	Carc. Cat 3
EU Annex	Carcinogenicity – category 2
ECHA	Carc. 2
ACGIH	Carcinogenicity – A3
DFG	Carcinogenicity – 3B
SCOEL	NA
HCOTN	NA
IARC	NA



Source	Notations
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
Insufficient data to assign a skin notation.

IDLH

Is there a suitable IDLH value available? Yes

Additional information

Molecular weight:	138.21
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 5.71 mg/m ³ ; 1 mg/m ³ = 0.175 ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> 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) (1977) Isophoron – MAK value documentation, German language edition.

European Chemicals Agency (ECHA) (2019) 3,5,5-trimethylcyclohex-2-enone – REACH assessment.

European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2013) 2-Cyclohexen-1-one, 3,5,5-trimethyl: Human health tier II assessment – IMAP report.

Nordic Expert Group for Criteria Documentation of Health Risks of Chemicals (1991) S-171
Isophorone. NR 1991 84.

Organisation for Economic Cooperation and Development (OECD) (2003) SIDS initial assessment
profile – 3,5,5-trimethylcyclohex-2-enone (Isophorone).

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).

UK Health and Safety Executive (HSE) (2002) EH40/2005 Workplace exposure limits.

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

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