

## 2-NITROPROPANE

**CAS number:** 79-46-9

**Synonyms:** Dimethylnitromethane, isonitropropane, nitroisopropane, 2-NP,  $\beta$ -nitropropane

**Chemical formula:**  $C_3H_7NO_2$

**Structural formula:** —

### Workplace exposure standard (retained)

**TWA:** 10 ppm (36 mg/m<sup>3</sup>)

**STEL:** —

**Peak limitation:** —

**Notations:** Carc. 1B

**IDLH:** 100 ppm

**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 ppm (36 mg/m<sup>3</sup>) is recommended to protect for adverse central nervous system (CNS) effects, liver damage and potential carcinogenicity in exposed workers.

Given the limited data available from the primary sources about carcinogenicity outcomes in humans and the mechanism of action for carcinogenicity, it is recommended that additional sources are investigated at the next scheduled review.

### Discussion and conclusions

2-Nitropropane is used as a solvent, in the food industry and as an additive to rocket fuel and explosives.

Critical effects of exposure are adverse CNS effects and liver damage as observed in exposed workers. Carcinogenic potential associated with liver damage is demonstrated in chronically exposed rats (ACGIH, 2018; DFG, 1992).

Workplace exposures of 10 to 30 ppm are not associated with toxicity; whereas headache, nausea and anorexia are reported at exposures between 20 and 45 ppm (ACGIH, 2018; HCOTN, 1999). Liver carcinogenicity is evidenced above 25 ppm in chronically exposed rats but is unaffirmed in the available human epidemiological data (ACGIH, 2018; DFG, 1992; HCOTN, 1999; SCOEL, 2017). Genotoxicity *in vitro* and *in vivo* is not associated with a carcinogenic mechanism of action, but conclusive mechanistic investigations are not identified and role of hypothetical genotoxic metabolites appears plausible (IARC, 1999).

Prevention of liver damage is suggested to be protective of subsequent liver carcinogenicity (ACGIH, 2018). However, a threshold for liver damage and resulting carcinogenicity at 25 ppm in chronically exposed rats is disputed in the available source material (ACGIH, 2018; SCOEL, 2017). In view of the

absence of toxicity at exposures between 10 and 20 ppm in the workplace, the TWA of 10 ppm (SWA, 1991 and ACGIH, 2001) is recommended to be retained.

Due to the equivocal evidence for carcinogenicity in humans and genotoxicity in animals, it is recommended additional data sources are reviewed for these endpoints at subsequent reviews.

## **Recommendation for notations**

Classified as a category 1B 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.

There are insufficient data to recommend a skin notation.

## APPENDIX

### Primary sources with reports

Source	Year set	Standard
<b>SWA</b>	<b>1991</b>	<b>TWA: 10 ppm (36 mg/m<sup>3</sup>)</b>
<b>ACGIH</b>	<b>2001</b>	<b>TLV-TWA: 10 ppm (36 mg/m<sup>3</sup>)</b>
<p>TLV-TWA intended to protect for liver damage and potential liver cancers.</p> <p>Classified as confirmed carcinogen in animals with unknown relevance to humans (A3).</p> <p>Summary of data:</p> <p>TLV-TWA based on weight of evidence of liver cell hypertrophy and cancer in rats, suggestive but inconclusive increased cancer incidence in epidemiological study and mutagenicity <i>in vitro</i> in bacteria. Exposure that causes liver damage in rats associated with increased cancer incidence, protection for liver damage therefore also expected to be protective of cancer.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>• Liver damage and death reported for exposed tank painters (exposures not measured)</li> <li>• Prolonged repeated exposure at 20–45 ppm associated with nausea, vomiting, diarrhoea, anorexia and severe headache (no further details provided)</li> <li>• 4 deaths from cancer in each males (n=1,334) and females (n=147) compared with 1 and 0.8 expected, respectively, reported in retrospective mortality study of production workers (n=1,481); lack of individual exposure data, workers with long exposures and small number of deaths in the groups limited conclusive evaluation of this study, but results suggest association: <ul style="list-style-type: none"> <li>◦ follow-up study showed no excess in liver cancer or liver disease mortality.</li> </ul> </li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>• LC<sub>50</sub>: 400 ppm (rats, 6 h); LC<sub>Lo</sub>: 1,513 ppm (rats, 4.5 h)</li> <li>• Methaemoglobin levels at 750 ppm (4.5 h) and 280 ppm (7 h) were 25% and 10–15%, respectively (cats)</li> <li>• Dyspnoea and mortality at 328 ppm (cats, 7 h/d, 5 d); histopathology showed degeneration of liver, heart and kidney: <ul style="list-style-type: none"> <li>◦ no histopathological changes in monkeys, rabbits, guinea pigs and rats at 328 ppm independent of duration (7 h/d, 5 d/wk, 191 d, also cited in DFG, 1992)</li> </ul> </li> <li>• Hepatocellular carcinoma or adenoma at 207 ppm (rats only) in chronic inhalation study with dose groups 0, 27, 207 ppm (rats, rabbits, 7 h/d, 5 d/wk, 6 mo); no tumours in any other groups/species: <ul style="list-style-type: none"> <li>◦ liver cell hypertrophy, hyperplasia and necrosis at 207 (rats) after 3 mo</li> </ul> </li> <li>• Liver tumours at 100 ppm in 3 controlled chronic inhalation studies with separate dose groups of 25, 100, 250 ppm (rats, 7 h/d, 5 d/wk, 22 mo): <ul style="list-style-type: none"> <li>◦ tumours occurred in males after 12 mo and after 18 mo in females</li> <li>◦ NOAEL: 25 ppm for substance-related effects including tumorigenicity</li> </ul> </li> <li>• Genotoxic <i>in vitro</i> in bacteria and reacts with DNA <i>in vitro</i>; non-mutagenic in <i>in vivo</i> assays with <i>D. melanogaster</i>, rats and mice</li> <li>• Metabolic denitrification causes methaemoglobin formation and increase nitrite concentrations in tissue; oxidised to acetone and nitrite in the liver</li> <li>• 40% absorption of inhaled doses of 20 and 154 ppm (rats, 6 h); 50% exhaled as CO<sub>2</sub>, 15% in excreta within 48 h.</li> </ul>		

Source	Year set	Standard
Insufficient data to recommend a TLV-STEL or notations for skin absorption or sensitisation.		
<b>DFG</b>	<b>1992</b>	<b>Not assigned</b>
<p>Summary of additional data:</p> <p>MAK not assigned based on positive liver tumorigenicity in rats and positive mutagenicity in bacteria and liver cells.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>No additional data presented.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Liver is target organ of carcinogenic activity as shown in controlled repeat oral dose study at 89 mg/kg/d (rats, n=22, 3 times/wk, 16 wk, 77 wk observation period); liver tumours reported in all animals and 4 had lung metastases</li> <li>Dose-dependent liver carcinogenesis affirmed at dose range 25–125 ppm in controlled repeat inhalation study with tumour promotion using 10 mg/kg Clophen A50 (rats, 6 h/d, 5 d/wk, 3 wk)</li> <li>Mutagenic mechanism of action in bacteria, rat hepatocytes and V79 cells suspected to be associated with ineffective reductive metabolism to acetone oxime, which hinder DNA repair: <ul style="list-style-type: none"> <li>DNA repair not impaired by metabolites of oxidative metabolism</li> <li>distributed evenly to all organs <i>in vivo</i>, but DNA damaging products likely to form only from metabolism in the liver (rats)</li> <li>increased DNA repair observed in rat liver cells <i>in vivo</i> at 20–80 mg/kg.</li> </ul> </li> </ul>		
<b>SCOEL</b>	<b>2017</b>	<b>Not assigned</b>
<p>Summary of additional data:</p> <p>TWA not assigned due to suspected genotoxic carcinogenicity. Kinetic studies indicate that two separate metabolic pathways are significant to observed liver carcinogenicity. Exact mechanism of action is unclear but cannot be excluded that it is relevant to human exposure.</p> <p>Due to likely non-threshold mechanism of action, cancer risk limit values are derived from a 22 mo chronic inhalation study in rats (also cited in ACGIH, 2018); tumour risk of 1:10,000 calculated as 0.017 ppm (0.0644 mg/m<sup>3</sup>).</p> <ul style="list-style-type: none"> <li>BMD not calculable from available study due to only 1 exposure group</li> <li>Extrapolation to lifetime study (104 wk) accounting for survival rates arrives at tumour incidence 25% (T25) dose of 25.3 ppm or 78.8 mg/m<sup>3</sup> (rats)</li> <li>Conversion to human T25 (hT25) assuming 75 yr lifespan and working 48 wk/yr for 40 yr and no interspecies adjustment arrives at hT25: 51.3 ppm or 160.1 mg/m<sup>3</sup></li> <li>Linear extrapolation to a chosen risk number (R) by substituting 4 x hT25 x R arrives at a 1:10,000 risk number of 0.017 ppm or 0.0644 mg/m<sup>3</sup>.</li> <li>Skin absorption study (10 min and 60 min) indicated high permeability; skin notation recommended to minimise absorption of a genotoxic carcinogen.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Chronic 22 mo inhalation study at 25 ppm in rats (also cited in ACGIH, 2018) re-examined; 25 ppm not considered NOAEL (as cited in ACGIH, 2018) based on adverse liver histopathology (increased focal areas of hepatocellular nodules) and low survival rate in treated group compared with control (56/250 versus 111/250) and considered to be consistent with carcinogenicity.</li> </ul>		



Source	Year set	Standard
<b>OARS/AIHA</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>HCOTN</b>	<b>1999</b>	<b>TWA: 1 ppm (3.6 mg/m<sup>3</sup>)</b>
<p>Summary of additional data:</p> <p>Sufficient evidence for carcinogenicity in rats, but not in humans; available epidemiological data inadequate for quantitative assessment. Incidence of liver tumours at 25 ppm in chronic inhalation study with rats (also cited in ACGIH, 2018 and SCOEL, 2017) used as starting point to calculate carcinogenic activity:</p> <ul style="list-style-type: none"> <li>Calculated concentration attributable to lifetime carcinogenicity is <math>5.6 \times 10^{-3}</math> mg/m<sup>3</sup> (rats): <ul style="list-style-type: none"> <li>accounts for tumour incidence in exposed (13/249) and control animals (3/250), average rat lifespan (1,000 d), exposure period (7 h) and experimental period (665 d)</li> </ul> </li> <li>Additional lifetime cancer risk in humans calculated from <math>5.6 \times 10^{-3}</math> mg/m<sup>3</sup>: <ul style="list-style-type: none"> <li>assuming working period (5 d/wk, 48 wk/y, 40 y), shift duration (8 h) and respiratory volume (10 m<sup>3</sup>)</li> <li>additional risk of <math>4 \times 10^{-5}</math> at 0.036 mg/m<sup>3</sup> or <math>4 \times 10^{-3}</math> at 3.6 mg/m<sup>3</sup>.</li> </ul> </li> </ul> <p>Human data:</p> <ul style="list-style-type: none"> <li>Headache, nausea and anorexia at daily occupational exposure of 20–45 ppm; no effects at 10–30 ppm (4 h/d, 3 d/wk, also cited in ACGIH, 2018).</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>NOAEL: 10 mg/kg/d for liver damage in repeat gavage study (rats, 5 d/wk, 4 wk); LOAEL: 50 mg/kg/d</li> <li>Generally non-mutagenic, but strong evidence for DNA repair inhibition <i>in vitro</i> and <i>in vivo</i> in rat hepatocytes.</li> </ul>		

## Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✓ 2013	<ul style="list-style-type: none"> <li>Critical effects are carcinogenicity and potential mutagenic effects; expected to have acute inhalational toxicity</li> <li>Classified as category 2 carcinogen based on positive carcinogenicity in animal studies: <ul style="list-style-type: none"> <li>available epidemiological studies are inconclusive</li> </ul> </li> <li>Low potential for bioaccumulation; <math>t_{1/2} &lt; 2</math> h (rats)</li> <li>Limited dermal absorption based on high recovery of dermal dose following dermal application experiment (monkeys, 12 h)</li> <li>No signs of toxicity at 2,000 mg/kg as dermal dose on abraded skin (rabbits, 24 h).</li> </ul>
IARC	✓ 1999	<ul style="list-style-type: none"> <li>No adequate epidemiological data available</li> <li>Carcinogenic in rats <i>via</i> oral and inhalational routes; liver cancers evidenced in 2 inhalation studies (also cited in ACGIH, 2018 and DFG, 1992)</li> <li>Potential genotoxic mechanism of action hypothesised to act <i>via</i> metabolic formation of propane 2-nitronate, which is more mutagenic in <i>Salmonella</i> than 2-nitropropane</li> <li>Classified as Group 2B carcinogen, possibly carcinogenic to humans.</li> </ul>
US EPA	✓ 1991	No additional data.



Source	Year	Additional information
ECHA	✓ 2019	No additional data.
OECD	✓ 2010	No additional data.
US NIOSH	✓ 1994	IDLH based on acute inhalation toxicity data in animals.

## Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?

Yes

Is the chemical carcinogenic with a mutagenic mechanism of action?

Insufficient data

**Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.**

## Notations

Source	Notations
SWA	Carc. 1B
HCIS	Carcinogenicity – category 1B
NICNAS	Carc. Cat. 2
EU Annex	Carcinogenicity – category 1B
ECHA	Carcinogenicity – category 1B
ACGIH	Carcinogenicity – A3
DFG	Carcinogenicity – 2
SCOEL	Carcinogenicity – A, Skin
HCOTN	—
IARC	Carcinogenicity – Group 2B
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:

Dermal LD<sub>50</sub> ≤ 1000 mg/kg:

Dermal repeat-dose NOAEL ≤ 200 mg/kg:

Dermal LD<sub>50</sub>/Inhalation LD<sub>50</sub> < 10:

*In vivo* dermal absorption rate > 10%:

Estimated dermal exposure at WES > 10%: **yes**

**insufficient data to assign a skin notation**

## IDLH

Is there a suitable IDLH value available? Yes

## Additional information

Molecular weight:	89.09
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 3.6 mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = 0.28 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 7<sup>th</sup> 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) (1992) 2-Nitropropane – MAK value documentation.

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) (1999) 2-Nitropropane. Health based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 1999/13OSH.

International Agency for Research on Cancer (IARC) (1999) Volume 71, Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2013) Propane, 2-nitro: Human health tier II assessment – IMAP report.

Organisation for Economic Cooperation and Development (OECD) (2010) SIDS Final assessment profile –Nitroparaffins.

Tenth Adaptation to Technical Progress Commission Regulation (EU) 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).



US Environmental Protection Authority (US EPA) (1991) Integrated Risk Information System (IRIS)  
Chemical Assessment Summary – 2-nitropropane.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to  
life or health concentrations – 2-nitropropane.

DRAFT