

2 - NITROTOLUENE

CAS number: 88-72-2

Synonyms: o-Nitrotoluene; o-methylnitrobenzene;
2-methylnitrobenzene; nitrophenylmethane; nitrotoluol

Chemical formula: $C_7H_7NO_2$

Workplace exposure standard (amended)

TWA: 0.45 ppb (2.54 $\mu\text{g}/\text{m}^3$)

STEL: —

Peak limitation: —

Notations: Carc. 1B

IDLH: —

Sampling and analysis: There is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 0.45 ppb (2.54 $\mu\text{g}/\text{m}^3$) is recommended to protect for excess cancers in exposed workers.

Given the limited data available about inhalation exposure from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

2-Nitrotoluene is used in the manufacture of agricultural chemicals and rubber and in the manufacture of various dyes for wool, silk leather and cotton.

Based on evidence in animals, 2-nitrotoluene is characterised as a non-threshold based genotoxic carcinogen by the ACGIH (2018), DFG (1993), NICNAS (2013) and US EPA (2008). Based on evidence in animals, it is considered to be a carcinogen with potential to cause cancer in humans (DFG, 1993; NICNAS, 2013). However, the mode of action for tumour formation is unknown (US EPA, 2008).

The recommended TWA of 0.45 ppb is derived at a minimal cancer risk level using a cancer slope factor. This value is based on dose-response data from oral exposure in animal studies and adjusted to account for differences humans and experimental animals (US EPA, 2008).

It is noted that oral exposure may enhance the genotoxicity of 2-nitrotoluene, likely due to action of intestinal bacteria. Therefore, the TWA based on oral studies is conservative for inhalational exposure because 2-nitrotoluene will bypass the potential effect of bacteria, resulting in a less potent genotoxic effect.

Recommendation for notations

Classified as a category 1B carcinogen according to the Globally Harmonized System of Classification and Labelling on Chemicals (GHS).

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

There are insufficient data to recommendation a skin notation.

DRAFT

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	Year	TWA: 2 ppm (11 mg/m³)
ACGIH	2001	TLV-TWA: 2 ppm (11 mg/m³)
TLV-TWA is intended to protect for methemoglobinemia and resultant anoxia and cyanosis in workers exposed to 2-, 3- and 4-nitrotoluene. Summary of information: Human data: - Limited data available - Capable of forming methemoglobin as aromatic, nitrogen-containing compounds - Cases of poisoning are not common - Considered only slightly toxic in comparison to nitrobenzene, based on anemiagenic potential - TLV-TWA based on aniline by structural analogy (no further information provided). Animal data: - Comparative study of the three nitrotoluene isomers (2-, 3- and 4-) in the diet of rats and mice (13 wk) reported more pronounced effects for exposure to 2-nitrotoluene (2,500 ppm) including toxicities in the liver, spleen and kidneys - liver weights increased at 625 ppm - The same study reported peritoneal mesothelioma in male rats fed 5,000 ppm - Three isomers not mutagenic in <i>Salmonella typhimurium</i> strains. Skin notation recommended due to structural similarity to nitrobenzene and aniline, which induce cyanosis upon dermal contact. However, no quantitative data on dermal absorption of nitrotoluene is available.		
DFG	1993	MAK: NA
No MAK value recommended because the substance is characterised carcinogenic. Summary of additional information: - Low acute toxicity - Main symptoms are intoxication of the CNS and metHb formation - Does not irritate the skin or eyes. Human data: - Limited reliable data available - Reported from a 1955 chemical industry document (no further details provided): 1,140 mg/m³ (60 min) leads to marked toxic effects - brief exposure at 228 mg/m³ caused symptoms of illness 5.7 mg/m³ considered a threshold. Animal data: - Chamber study: 1,086 mg/m³ (rat, 8 h); no symptoms reported		

Source	Year set	Standard
- LD₅₀: 890 mg/kg (rats, oral) - NOEL in rats ≈180 mg/kg/d (liver effects) - NOEL in female mice 631 mg/kg/d; male mice 106 mg/kg/d. Carcinogenicity notation: - Feeding study: mesothelioma (<i>tunica vaginalis</i>) in 3/19 male rats (353 mg/kg, 13 wk) - Mesothelioma is a rare condition also associated with exposure to <i>o</i>-toluidine, a structurally similar compound, indicating a common mechanism of tumour development. Germ cell mutagen category 3B based on evidence of genotoxicity (unscheduled DNA synthesis) in rats <i>in vivo</i>.		
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
NICNAS	✓ 2013	- The main critical effects to human health are genotoxicity, carcinogenicity and potential reproductive/fertility effects - Acute toxicity studies did not cause either mortality or toxicity following exposure at 5,000 mg/kg in rats or 2,000 mg/kg in rabbits - Mutagenic in somatic cells classified as a Category 2 Mutagenic Substance - LOAEL for chronic toxicity 625 ppm (25 mg/kg/d and 30 mg/kg/d in males and females, respectively) based on lesions observed in liver, bone marrow, spleen and lung - NOAEL for reproductive toxicity in rats was 179 mg/kg/d.
US EPA	✓ 2008	- Strong evidence for genotoxic carcinogenicity in rats and mice - Evidence that oral exposure might enhance the genotoxicity of 2-nitrotoluene because of action of intestinal bacteria - Provisional oral slope factor of 2.2×10^{-1} (mg/kg/d)⁻¹ based on dose-response data from a dietary study in rats (24 mo) reporting incidences of subcutaneous skin fibroma or fibrosarcoma.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? Yes

Is the chemical carcinogenic with a mutagenic mechanism of action? Yes

The chemical is a non-threshold based genotoxic carcinogen.

Is a cancer slope factor or inhalation unit risk value available? Yes

Cancer slope factor (1/(mg/kg/day))

2.2 x 10⁻¹

Calculated TWA value (µg/m³)

2.54

Notations

Source	Notations
SWA	Carc. 1B
HCIS	Carcinogenicity – category 1B
NICNAS	Carc. Cat. 2
EU Annex	NA
ECHA	NA
ACGIH	Skin
DFG	Carcinogenicity – 2
SCOEL	NA
HCOTN	NA
IARC	Carcinogenicity – Group 3
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?

No, the chemical is a genotoxic carcinogen

Additional information

Molecular weight:	137.14
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 5.6 mg/m ³ ; 1 mg/m ³ = 0.18 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) (1993) 2-Nitrotoluene – MAK value documentation.

International Agency for Research on Cancer (IARC) (1996) 2-nitrotoluene. IARC Monographs on the evaluation of the carcinogenic risk to humans. VOL: 65.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2013) Benzene, 1-methyl-2-nitro-: Human health tier II assessment – IMAP report.

US Environmental Protection Agency (US EPA) (2008) Provisional Peer Reviewed Toxicity Values for o-Nitrotoluene (2-Nitrotoluene) (CASRN 88-72-2). EPA/690/R-08/018F Final.