# Nitrotoluene, 3- and 4- Isomers

| CAS number: | 99-08-1 (3-Nitrotoluene [meta])  99-99-0 (4-Nitrotoluene [para]) |
| --- | --- |
| Synonyms: | Mononitrotoluene, methylnitrobenezene, nitrotoluol |
| Chemical formula: | C7H7NO2 |
| Structural formula: |  |

Workplace exposure standard (retained)

| TWA: | **2 ppm (11 mg/m3)** |
| --- | --- |
| STEL: | — |
| Peak limitation: | — |
| Notations: | **Sk.** |
| 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 TWA of 2 ppm (11 mg/m3) is recommended to protect for methemoglobinemia, reproductive effects and potential effects on the liver, spleen and kidneys effects in exposed workers.

## Discussion and conclusions

This evaluation reviews the available data for two isomers of nitrotoluene: 3-nitrotoluene & 4‑nitrotoluene. 2-nitrotoluene has been evaluated separately.

3-nitrotoluene is used in the manufacture of agricultural and rubber chemicals. It is also used in various dyes for cotton, wool, silk, leather and paper and in azo and sulfur dye. 4-Nitrotoluene is produced in negligible quantities.

Critical effects of exposure are methaemoglobinaemia and resultant anoxia and cyanosis. Limited data also indicate a potential for hepatic, renal and reproductive damage of varying degrees. Carcinogenic effects in animals are also noted.

Limited data is available in humans. These chemicals, as aromatic, nitrogen-containing materials, can form methaemoglobin with the potential to induce resultant effects associated with methaemoglobinaemia. ACGIH (2018) recommend a TWA of 2 ppm for nitrotoluene isomers based on analogy to aniline. Effects on the liver, spleen and kidneys to varying degrees have been identified in oral studies in rats. All isomers were associated with impaired testicular function and increased time of the oestrus cycle in rats (ACGIH, 2018; DFG, 1993; HCOTN, 2004). HCOTN (2004) recommend a health-based OEL for 3-Nirotoluene of 2 mg/m3 (0.4 ppm) based on effects on the spleen in rats. Evidence in animals suggest a carcinogenic potential (DFG, 1993). However, the cancers reported in animals are not relevant for humans and there is a lack of data available to confirm this effect in humans through the inhalational route. Therefore, cancer is not a critical effect in recommending a TWA.

The TWA of 2 ppm (11 mg/m3) by ACGIH (2018) is recommended to protect for methaemoglobinaemia and resultant anoxia and cyanosis.

## Recommendation for notations

3-Nitrotoluene and 4-Nitrotoluene are not classified as carcinogens according to the Globally Harmonised 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 and by analogy to structurally similar chemicals.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA Year TWA: 2 ppm (11 mg/m3) |
| TWA for 3-Nitrotoluene (99-08-1) and 4-Nitrotoluene (99-99-0). |
| ACGIH 2001 TLV-TWA: 2 ppm (11 mg/m3) |
| TLV-TWA recommended for the isomers of nitrotoluene (3-Nitrotoluene & 4‑Nitrotoluene) is intended to protect against methaemoglobinaemia and resultant anoxia and cyanosis.  Summary of data:  Review of ortho-meta, and para isomers of nitrotoluene. TLV set by analogy to the TLV for aniline.  Human data:   * Exposure to all isomers has potential for induction of methaemoglobin as aromatic, nitrogen-containing compounds * Cases of poisoning not common * Considered only slightly toxic; relatively low in anaemiagenic potential * Considered 1-nitrotoluene to present a lesser hazard than the other isomers * TLV-TWA based on recommendations from a study suggesting TLV of 5 ppm for the 3‑Nitrotoluene & 4-Nitrotoluene; which in turn was based on TLV-TWA for aniline at the time; no further information.   Animal data:   * Comparative study of nitrotoluene isomers; 0, 625, 1,250, 2,500, 5,000 or 10,000 ppm in the diet of rats and mice for 13 wk: * 3-Nitrotoluene: 625 ppm produced renal damage in male rats; ≥2,500 ppm histopathologic damage in the spleens of the male and female rats; no effects in mice * 4-Nitrotoluene: 10,000 ppm bw depression in both species; all doses caused significant lesions in rat kidney and spleen; histopathologic changes in mice * all isomers associated with impaired testicular function and increased length of the oestrus cycle in rats but no reproductive effects observed in mice.   Genotoxicity   * Three isomers not mutagenic in *S. typhimurium* strains TA100, TA1535, TA1537 and TA98 * 4-Nitrotoluene caused mutations in mouse lymphoma L5178Y test with metabolic activation * Unscheduled DNA synthesis not increased in male rats given 3-Nitrotoluene or 4‑Nitrotoluene * Nitrotoluene induced s-phase DNA synthesis in hepatocytes of rats but not in those of mice.   Skin notation assigned due to structural analogy to aniline and nitrobenzene. Insufficient data to recommend sensitiser or carcinogenicity notations or a TLV-STEL. |
| DFG 1993 / 2006 MAK: NA |
| No MAK value recommended due demonstrated carcinogenicity in animals.  **3-Nitrotoluene:**   * Odour threshold in humans 0.045 ppm * Low acute toxicity * Single occlusive application at 1,157 mg/kg on the skin of male and female rats; 24 h caused poor general condition but no deaths * Slightly increased respiration rate in 1 rabbit, 50 h after single occlusive application at 532 mg/kg * Model calculated dermal absorption of 0.006 mg/cm2/h * No carcinogenicity study with 3‐nitrotoluene available: however, it is classified analogous to 4‐nitrotoluene in carcinogen category 3B * No MAK due to suspected carcinogenicity * Additional carcinogenic risk is assumed based on calculated absorption quantities and the demonstrated dermal penetration *in vivo.*   **4-Nitrotoluene:**   * 2-yr study in diet in rats; equivocal evidence of carcinogenic activity in the male rats and some evidence in the females: * 0, 55, 110, 240 mg/kg/d males; subcutaneous tumours, intermediate but not high dose * 0, 60, 125, 265 mg/kg/d females; clitoral gland tumours, intermediate but not high dose * 2-yr study in diet in mice: * 0, 170, 345, 690 mg/kg/d males; highest concentration increased the incidence of alveolar or bronchiolar tumours * 0, 155, 315, 660 mg/kg/d females; no carcinogenic effects * No mutagenic effects in valid mutagenicity tests using different strains of *S. typhimurium* and *E. coli* in the presence and absence of a metabolic activation system * UDS test negative in primary rat hepatocytes and rat spermatocytes * Inactive in a number of valid *ex vivo* UDS tests in rats. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2004 1 ppm (6 mg/m3) 3-Nitrotoluene |
| 3-Nitrotoluene  Administrative OEL; health-based OEL (HBROEL) of 2 mg/m3 (0.4 ppm) recommended based on effects in spleen in rats  Summary of additional data:   * 13-wk oral diet study in rats reported a LOAEL of 48 mg/kg/d (lowest dose) for spleen lesions * Adjusted by 7/5 for continuous feeding study to 5-d work week =63 mg/kg/d * Factor of 4 for allometric scaling from rats to humans and overall factor of 36 to account for absence of a NOAEL, inter- and intraspecies variation, differences between experimental conditions and exposure pattern of the worker= 0.44 mg/kg/d * Applied to 70 kg worker inhaling 10 m3 of air over 8-h, 100% retention and rounding according to HCOTN methodology ≡2 mg/m3 (0.4 ppm). |

### Secondary source reports relied upon

NIL.

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | Insufficient data |
| --- | --- |
| 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 | NA |
| HCIS | — (4-Nitrotoluene)  NA (3-Nitrotoluene) |
| NICNAS | NA |
| EU Annex | — |
| ECHA | — |
| ACGIH | Skin |
| DFG | Carcinogenicity 3B, H (skin) |
| SCOEL | NA |
| HCOTN | * (3-Nitrotoluene) |
| 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: |  |  |  | | Dermal LD50 ≤1000 mg/kg: |  |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  | | Estimated dermal exposure at WES >10%: | yes | 2.00 |  | |  |  | 2  **insufficient data to assign a skin notation** | | |

### IDLH

| Is there a suitable IDLH value available? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | 137.13 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = Number mg/m3; 1 mg/m3 = 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*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2006) 3-Nitrotoluene – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2006) 4-Nitrotoluene – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2004) 3-Nitrotoluene. Health-based recommendation on occupational exposure limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/135.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – Nitrotoluene (o-, m-, p-isomers).