M-TOLUIDINE

CAS number: 108-44-1

Synonyms: 1-Amino-3-methylbenzene, 3-aminotoluene, 3-methylaniline, 3-methylbenzenamine

Chemical formula: C_7H_9N

Workplace exposure standard (interim)

TWA: **2 ppm (8.8 mg/m^3)**

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **—**

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 (8.8 mg/m^3) is recommended in the interim to protect for methaemoglobinemia and irritation of the eyes, kidney and bladder in exposed workers.

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

Discussion and conclusions

m-Toluidine and its hydrochloride (HCl) salt are used as intermediates in dye and chemical manufacture.

The critical effects of exposure are methaemoglobinemia and irritation of the eyes, kidney and bladder.

Substance-specific exposure data are limited. Toluidine isomers (*m-, o-, p-*) are reported to elicit methaemoglobinemia, painful urination and haemoglobinuria analogously to aniline (ACGIH, 2018). Signs of illness, which are not specified in the available source material (ACGIH, 2018; ECHA, 2020), are associated with air concentrations of 10 ppm of toluidine isomer mixtures; concentrations above 5 ppm are considered unsatisfactory in an industrial survey (ECHA, 2020). Methaemoglobinemia is reported at 30 mg/kg/day by gavage in a sub-chronic reproductive study with rats; an experimentally determined NOAEL for this effect is not reported in the available source material (ECHA, 2020). No evidence for carcinogenic activity is found in chronically fed rats, whereas equivocal evidence is demonstrated in mice (ACGIH, 2018).

In the absence of sufficient exposure data, ACGIH (2018) recommends a TLV-TWA of 2 ppm and skin notation based on analogies to toxicologically and structurally similar aniline, for which the critical endpoint is also methaemoglobin formation. ACGIH does not appear to consider the results of a sub-chronic reproductive study reported by ECHA (2020) and OECD (2001) in the assessment. In view of this uncertainty, the current SWA TWA of 2 ppm is retained in the interim and further assessment of

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additional sources is recommended during subsequent reviews of the WES. Aniline is structurally and toxicologically related to *m*-toluidine; therefore, subsequent reviews should consider the TWA of 0.5 ppm for aniline and its homologues, which protects for methaemoglobinaemia and is based on the results of a volunteer study with repeat oral doses of aniline (SCOEL, 2010).

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.

A skin notation is recommended due to evidence of dermal absorption and contribution to adverse systemic effects.

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APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 2 ppm (8.8 mg/m^3)***
ACGIH	***2001***	***TLV-TWA: 2 ppm (8.8 mg/m^3)***

TLV-TWA intended to protect for irritation of the eyes, kidneys and bladder, methaemoglobinemia, anaemia and cyanosis.

Summary of data:

m-Toluidine has a similar toxicity profile to *o*-toluidine, for which more toxicological data are available. TLV-TWA based on analogy to aniline and *o*- and *p*-toluidine.

Human data:

- Toluidine isomers (not specified) produce same symptoms as aniline, but with less cyanosis, which include methaemoglobinemia, painful urination and haemoglobinuria
- Severe intoxication at 40 ppm and unspecified illness at 10 ppm of a mixture of toluidine isomers (not specified) reported (1 h, no further details provided)
- No epidemiological data available for exposure to *m*-toluidine alone.

Animal data:

- LD_{50}: 450 mg/kg (rats, oral)
- Maximal mean methaemoglobinemia of 60% produced from single IV injection of 27 mg/kg (cats)
- No significant increase in tumour incidence reported in chronic feeding study, in which animals were fed diets containing the *m*-toluidine HCl salt at 8,000 ppm (3 mo) followed by 4,000 ppm (15 mo), or 16,000 ppm (3 mo) followed by 8,000 ppm (15 mo) (rats, 18 mo)
- Significant increase in hepatic tumours (low-dose males only) reported in chronic feeding study, in which animals were fed diets containing the *m*-toluidine HCl salt at 16,000 ppm (males and females, 5 mo) followed by 4,000 ppm (males, 13 mo) or 8,000 ppm (females, 13 mo), or 32,000 ppm (males and females, 5 mo) followed by 8,000 ppm (males, 13 mo) or 16,000 ppm (females, 13 mo) (mice, 18 mo):
  - increased incidence of hepatic tumours only observed in male low-dose group
  - no evidence for dose-dependence (no further details provided)
  - m-toluidine considered not classifiable as human carcinogen by ACGIH
- Non-mutagenic *in vitro* in bacteria or rat hepatocytes in the presence or absence of metabolic activation
- No evidence for changes in DNA synthesis in testes at 200 mg/kg or in pup livers following parenteral injection of an acute lethal dose (mice)
- Rodents are less susceptible to chemically induced methaemoglobinemia than humans.

Insufficient data available to recommend a TLV-STEL or sensitiser notation.

Not classifiable as a human carcinogen based on results of chronic feeding studies with mice and rats.

A skin notation is recommended by analogy to *o*-toluidine, dermal absorption of which contributes to total systemic burden.

A BEI for metHb inducers is available.

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Source	Year set	Standard
DFG	***NA***	***NA***
No report.		
SCOEL	***NA***	***NA***
No report for m-toluidine. Human data for *aniline* (reported in SCOEL, 2010): • Blood methaemoglobin concentrations levels of ≈5% considered tolerable by analogy to carboxyhaemoglobin, for which 4% is tolerable • Methaemoglobin formation demonstrated in volunteer repeat oral dose study with aniline dose groups 5, 15, 25, 35, 45, 55 and 65 mg/person/d (n=5/group, 3 d): ○ increase in methaemoglobin formation non-significant up to 15 mg (1.2–1.8%) ○ doses of 35, 45, 55 and 65 mg aniline caused methaemoglobin levels of 3.7, 7.1, 5.2% and 16%, respectively ○ daily dose of 35 mg aniline, corresponding to 3.7% increase in blood methaemoglobin concentrations, used as basis for TWA of aniline (0.5 ppm ≡1.94 mg/m^3).		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source		Year	Additional information
ECHA	✓	2020	• Exposure at 40 ppm to mixture of isomers (1 h) caused severe intoxication, 10 ppm (prolonged period, not specified) may lead to signs of illness, unsatisfactory workplace conditions at >5 ppm reported in industrial survey (no further details provided, also cited by ACGIH, 2018) • LD_{50}: 1,000–1,030 mg/kg (rats, dermal) • LOAEL of 30 mg/kg for signs of methaemoglobinemia and haemolysis in spleens in repeat gavage reproductive study with dose groups 0, 30, 100 and 300 mg/kg/d (rats, >41 d): ○ reduced locomotor activity at 300 mg/kg/d ○ reduced RBC count, haemoglobin concentration and histopathological lesions in liver at 100 and 300 mg/kg/d • DNEL of 0.59 mg/m^3 based on LOAEL of 30 mg/kg/d for methaemoglobinemia in reproductive study; overall assessment factor of 45 applied to account for lack of experimentally determined NOAEL, differences in duration of exposure and inter- and intraspecies differences considering higher human susceptibility to methaemoglobinemia than rats.

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Source		Year	Additional information
OECD	✓	2001	• NOAEL of 30 mg/kg/d for increased implantation losses in reproductive gavage study (rats, also cited by ECHA 2020); death of pups at 100 mg/kg/d attributed to maternal anaemia during nursing, developmental NOAEL of 100 mg/kg/d • Agency considers non-mutagenic based on negative results in available *in vitro* and *in vivo* studies (also cited in ACGIH, 2018) • Carcinogenicity studies with mice and rats (also reported in ACGIH, 2018) considered inconclusive as they did not meet current carcinogenicity testing protocols.

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	Skin
HCIS	—
NICNAS	NA
EU Annex	—
ECHA	—
ACGIH	Carcinogenicity – A4, Skin
DFG	NA
SCOEL	NA
HCOTN	NA
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 LD_{50} ≤1000 mg/kg:	yes
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	
In vivo dermal absorption rate >10%:	
Estimated dermal exposure at WES >10%:	
	consider assigning a skin notation

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IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	107.16
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 4.38 mg/m^3; 1 mg/m^3 = 0.229 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.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2010) Recommendation from the Scientific Committee on Occupational Exposure Limits for aniline. SCOEL/SUM/153.

European Chemicals Agency (ECHA) (2020) m-Toluidine – REACH assessment.

Organisation for Economic Cooperation and Development (OECD) (2001) SIDS initial assessment profile – m-Toluidine.

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