P-TOLUIDINE

CAS number: 106-49-0

Synonyms: 1-Amino-4-methylbenzene, 4-aminotoluene, 4-methylaniline, 4-methylbenzenamine, 4-toluidine, p-tolylamine, p-aminotoluene

Chemical formula: C_7H_9N

Workplace exposure standard (interim)

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

STEL: **—**

Peak limitation: **—**

Notations: **Carc. 2, Sk., DSEN**

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

p-Toluidine and its hydrochloride salt are used as intermediates in dye and chemical manufacture.

Critical effects of exposure are methaemoglobinemia and irritation of the eyes, kidneys and bladder.

Substance-specific exposure data are limited, but the available database indicates toxicological similarities to structurally related aniline and other toluidine isomers (ACGIH, 2018; SCOEL, 2013). Evidence of painful urination, haemoglobinuria, dizziness and headache in humans exposed at 5 ppm is reported, but poorly documented (NICNAS, 2015). An approximately two-fold lower potential for methaemoglobin formation than aniline is reported in an acute intravenous dose study with cats (ACGIH, 2018; SCOEL, 2013). Evidence for carcinogenic potential in animals is equivocal (ACGIH, 2018) and the available mutagenicity data are inconclusive regarding a genotoxic mechanism of action (DFG, 2004; NICNAS, 2015). Systemic toxicity following dermal exposure and dermal sensitisation is reported in animal studies. Dermal sensitisation data in humans is inconclusive and a dermal sensitiser notation is disputed in the available source material (DFG, 2004; SCOEL, 2013).

In view of the limited toxicological database, SCOEL (2013) and ACGIH (2018) base their respective TWA recommendations of 1 and 2 ppm on analogy to the methaemoglobin-forming potential of aniline. SCOEL (2013) additionally recommends a STEL of 2 ppm to protect for acute irritation, the experimental basis of which is however not discussed. DFG (2004) does not recommend a numerical TWA equivalent due to potential genotoxic carcinogenicity. In view of these uncertainties, the current

SWA TWA of 2 ppm is retained in the interim and further assessment of additional sources is recommended during subsequent reviews.

A STEL is not recommended as there is no evidence for increased severity of effects within an order of magnitude of the recommended TWA.

Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser but not a respiratory sensitiser according to the GHS.

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

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 methaemoglobinemia and irritation of the eyes, skin, kidneys and bladder. Carcinogenicity confirmed in animal studies, but with unknown relevance to humans (A3). Skin notation recommended based on reports of systemic effects following dermal absorption in animals. A BEI for methaemoglobin inducers is available.

Summary of information:

p-Toluidine has a similar toxicity profile to *o*-toluidine, for which more toxicological data are available. Carcinogenic and mutagenic potential lower than that of *o*-toluidine based on animal studies. TLV-TWA based on analogy to aniline and *o*-toluidine.

Human data:

- Clinical signs of intoxication include methaemoglobinemia and haematuria (no further details provided)
- 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 *p*-toluidine alone
- Dermal permeability coefficient calculated as 0.0037 cm/h for intact human skin.

Animal data:

- Oral LD_{50} of 656 mg/kg (rats); 794 mg/kg (mice)
- LD_{50} of 890 mg/kg (rabbits, dermal)
- Positive dermal sensitisation reported in guinea pigs (no further details provided)
- URT and eye irritation, but no mortality at 640 mg/m^3 (rats, 1 h)
- Mean maximum methaemoglobinemia of 39.6% at 27 mg/kg IV injection (cats)
- No clinical signs of poisoning or gross lesions on autopsy in subchronic feeding study with dose groups 13.8, 66.8 and 125.7 mg/kg/d (rats, 4 wk, no further experimental details):
  - reduced body weight and increased liver weight at 66.8 and 125.7 mg/kg/d
- Equivocal results reported in chronic carcinogenicity studies with varying administration routes:
  - negative results and no signs of toxicity at 1,000 and 2,000 ppm of diet in feeding study (rats, 18 mo)
  - significant increases in hepatic tumours in feeding study with dose groups 1,000 ppm (6 mo) then 500 ppm (12 mo) and 2,000 ppm (6 mo) then 1,000 (12 mo) in males, significant increase in females only observed in high dose groups (mice, 18 mo, observed for 21 mo)
  - no increase in skin tumours in dermal application study (mice, 12 wk)
  - slight increase in malignant tumours at injection site and benign liver tumours, reduced body weight gain and hepatic necrosis, but unchanged survival compared to controls in lifetime subcutaneous injection study with dose groups 0, 25, 75 mg/kg (1 d/wk, 2 yr)
- Non-mutagenic in several *in vitro* assays with bacteria in the presence or absence of metabolic activation; increased single strand DNA breaks at 35 mg/kg IP injection (mice), inhibition of testicular DNA synthesis at 200 mg/kg gavage dose (mice).

Source	Year set	Standard
Insufficient data to recommend a TLV-STEL or sensitiser notation.		
DFG	***1990***	***Not assigned***

Summary of additional information:

MAK not established due to likely formation of mutagenic metabolites; mutagenic mechanism of carcinogenicity however not confirmed by conflicting evidence for mutagenicity and carcinogenicity in available animal data. Therefore, classified as 3B carcinogen. Despite toxicological similarities between *p*- and *o*-toluidine, available data for *p*-toluidine inadequate for assessment. Skin notation recommended based on systemic toxicity following dermal absorption in rabbits. Dermal sensitiser notation recommended based on positive result in sensitisation study with guinea pigs.

Human data:

- Absorbed through skin and mucous membranes and causes local irritation (no further details provided)
- Bladder papilloma detected in 2 workers in workplace study (n=81), 1 worker (age 23) exposed to only *p*-toluidine the other (age 49) to mixtures of *o*- and *p*-toluidine; air concentration of the mixture was 28.6 mg/m^3:
  - 6 cases of bladder tumours in 16 former employees exposed for 12–17 yr
- Positive sensitisation in patch test with patients (37/58) with existing sensitivity to *p*-phenylenediamine, DFG notes no information of clinical relevance of these findings.

Animal data:

- Moderately to highly irritating to rabbit skin and eyes (no further details provided)
- Positive sensitisation (mild erythema) when challenged with 0, 0.5, 1 and 2% solutions following induction with 2% solution as occlusive patch for 4 d. No sensitisation when challenged with 0.25% solution
- Positive sensitisation when challenged with 0, 0.1, 0.5, 1 and 2% solutions following induction with 0.5 g of 2% solution 2 wk prior.

SCOEL	***2013***	***TWA: 1 ppm; STEL: 2 ppm***

Summary of additional information:

MetHb formation critical effect in animals and humans. Quantitative inhalational data not available. Despite confirmed carcinogenic potential of *o*-toluidine, inadequate evidence available to classify *p*-toluidine as limited human epidemiological studies and equivocal animal carcinogenicity studies. Recommended OEL provisionally protects for methaemoglobinaemia in the absence of conclusive evidence for a carcinogenic effect. SCOEL notes that further assessment is required. Based on a 2-fold lower potential than aniline for MetHb formation reported in cats. OEL provisionally based on aniline (TWA for aniline of 0.5 ppm). Recommended TWA therefore 1 ppm. Appreciable increases in metHb formation are not expected during 15-min excursions at twice this value, STEL of 2 ppm therefore recommended, which is additionally expected to be protective of potential eye irritation observed in rabbits; the basis for protection against irritation is not discussed.

Human data:

- Odour threshold of 0.33 ppm
- Cross-sensitivity observed in patients sensitised to phenylene diamine; agency considers this evidence insufficient to recommend a sensitiser notation.

Human data for *aniline* (reported in SCOEL, 2010):

- Blood MetHb concentrations levels of ≈5% considered tolerable by analogy to carboxyhaemoglobin, for which 4% is tolerable
- MetHb formation reported in volunteer repeat oral dose study with aniline dose groups 0, 5, 15, 25, 35, 45, 55 and 65 mg/d (n=5/group, 3 d):

Source	Year set	Standard
		o increase in MetHb formation non-significant up to 15 mg (1.2–1.8%) o doses of 35, 45, 55 and 65 mg aniline caused methaemoglobin levels of 3.7, 7.1, 5.2% and 16%, respectively o daily dose of 35 mg aniline, corresponding to 3.7% increase in blood MetHb concentrations, used as basis for TWA of aniline (0.5 ppm ≡1.94 mg/m^3). Animal data: • MetHb levels of 4.2–6.6% after 3 mo, marginally higher after 6 mo at 40 mg/kg/d in chronic feeding study (rats, 6 mo). SCOEL regards this dose as the LOAEL • Substance half as potent in producing methaemoglobinaemia as aniline based on IV dose study (cats); cats are highly susceptible • MetHb concentrations up to 40% following dermal application for 2–6 h (rats) • Non-mutagenic *in vitro* in bacteria and mammalian cells; database for *in vivo* mutagenicity is limited, but positive result in *Drosophila* assay and potential formation of genotoxic metabolites indicate mutagenic potential *in vivo*. Insufficient data to recommend notations for carcinogenicity or sensitisation.
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2015	• Grouped assessment with corresponding HCl and sulfate salts • Human data indicates inhalation causes MetHb formation • Stranguria (painful urination), haemoglobinuria, dizziness and headache caused at ≥5 ppm, but with less pronounced cyanosis compared with aniline (no further details provided) • Information on genotoxicity insufficient for classification.
OECD	✓	2005	• Available carcinogenicity studies (also reported in all primary source documentation) limited by insufficient dose range, number of animals, exposure duration and level of documentation.

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	Carc. 2, Skin
HCIS	Carcinogenicity – category 2, Skin sensitisation – category 1
NICNAS	Carc. Cat. 3
EU Annex	Carcinogenicity – category 2, Skin sensitisation – category 1
ECHA	Carcinogenicity – category 2, Skin sensitisation – category 1
ACGIH	Carcinogenicity – A3
DFG	Carcinogenicity – 3B, H (skin), Sh (dermal sensitiser)
SCOEL	Skin
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:	yes
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%:	
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	107.15
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.

Deutsche Forschungsgemeinschaft (DFG) (1992) p-Toluidine – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2004) p-Toluidine – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2013) Recommendation from the Scientific Committee on Occupational Exposure Limits for 4-Aminotoluene (p-Toluidine). SCOEL/SUM/145.

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

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2015) p-Toluidine and its salts: Human health tier II assessment – IMAP report.

Organisation for Economic Cooperation and Development (OECD) (2005) SIDS initial assessment profile – p-Toluidine.

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).