



XYLIDINE (ALL ISOMERS)

CAS number: 1300-73-8

87-62-7

Synonyms: Aminodimethylbenzene, aminoxylene, dimethylaniline

Chemical formula: C₈H₁₁N

Workplace exposure standard (retained)

TWA: 0.5 ppm (2.5 mg/m³)

STEL: —

Peak limitation: —

Notations: Carc. 2, Sk.

IDLH: 50 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 0.5 ppm (2.5 mg/m³) is recommended to protect for methaemoglobinaemia and liver toxicity in exposed workers.

Given the data available from the primary sources about the relevance of carcinogenicity in humans, it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

Xylidine isomers are present as mixtures in raw materials used in the manufacture of dyes and pharmaceuticals.

The critical effects of exposure are methaemoglobinaemia and liver toxicity as observed in animals.

No quantitative human exposure data are reported in the available source material. Methaemoglobin (MetHb) formation due to internal exposure to the 2,6-xylidine metabolite, is reported in patients treated with lidocaine (DFG, 2003). Exposure below 5 ppm is recommended to prevent unsatisfactory working conditions in one investigation of industrial exposures. However, no further justification of this value is provided (ACGIH, 2018). In animals, all isomers share the same toxic endpoints. Their potency varies slightly (NICNAS, 2015; OECD, 2012). A NOAEC of 7.8 to 17.4 ppm for liver toxicity is reported in sub-chronic inhalation studies with various model species (ACGIH, 2018). For all isomers except 2,6-xylidine, a NOAEL of 2 mg/kg/day for hepatotoxicity is reported in sub-chronic feeding study in dogs (ACGIH, 2018) which is considered the LOAEL for 2,6-xylidine by OECD (2012).

Carcinogenicity is reported in rats chronically exposed at 15 to 150 mg/kg/day of 2,6-xylidine in the diet; however, no information on the dose response is available (DFG, 2003). The mutagenic potential of the pure substances is equivocal (ACGIH, 2018; DFG, 2003; HCOTN, 2002) and the human relevance of the carcinogenic endpoint is disputed in the available source material (ACGIH, 2018; DFG, 2003; HCOTN, 2002).

Based on the weight of evidence of the available animal exposure studies, ACGIH (2018) recommends a TWA equivalent of 0.5 ppm, which is expected to be sufficiently low to protect for methaemoglobinaemia, liver toxicity and potential carcinogenicity. However, due to the absence of a dose-response relationship for carcinogenicity in animals in the available database, DFG (2003) does not recommend a numerical TWA equivalent. In view of the uncertainty about carcinogenicity of 2,6-xylidine and its relevance to humans, the TWA of 0.5 ppm is retained in the interim and expected to be protective of methaemoglobinaemia and liver toxicity. Further assessment of additional information regarding the carcinogenic potential of the substances should be prioritised during subsequent reviews of the WES.

Recommendation for notations

2,6-xylidine is classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). The other isomers are not classified as carcinogens according to the 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.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	1991	TWA: 0.5 ppm (2.5 mg/m³)
ACGIH	2002	TLV-TWA: 0.5 ppm (2.48 mg/m³)
<p>TLV-TWA intended to protect for liver toxicity, methaemoglobinaemia and potential carcinogenicity. Carcinogenicity notation recommended based on increased tumour incidence chronically exposed rats. Skin notation recommended based on CNS effects observed in cats following dermal application.</p> <p>Summary of information:</p> <p>Moderately resembles toxic profile of aniline. TLV-TWA based on weight of evidence of available animal toxicity data; LOAEL of 30 mg/kg/d for MetHb formation in cats (most sensitive species to this endpoint), NOAEL of 10 mg/kg/d in rats and NOAEC of 7.8 ppm and LOAEC of 17.4–45 ppm for hepatotoxicity in various species. Based on these data, TLV-TWA of 0.5 ppm expected to be protective, but no further justification of the value is reported. BEI for MetHb inducers is available.</p> <p>Human data:</p> <ul style="list-style-type: none"> • No reports of poisoning or epidemiological data available • Exposure at 40 ppm (1 h) considered to cause severe toxic effects in humans, chronic exposure >5 ppm would indicate unsatisfactory conditions according to US NIOSH review (no further details provided). <p>Animal data:</p> <ul style="list-style-type: none"> • 2,5- and 3,5-xylydine most active MetHb inducers in cats, no significant differences in MetHb producing potential of other isomers: <ul style="list-style-type: none"> ◦ single IV injection of 30 mg/kg 2,4-xylydine produced mean MetHb levels of 6.3% compared with 61.6% produced by same amount of aniline (cats, n=15) • NOAEL of 10 mg/kg/d of 2,4-xylydine for dose-dependent liver damage and decreased liver function in repeat gavage study with dose groups 0, 10, 25, 50, 100, 250 and 400 mg/kg/d (rats, 7 d); severe bile duct hyperplasia and liver cell enlargement and necrosis reported at 400 mg/kg/d • Increased liver weight at 20, 100 and 500–700 mg/kg/d of 2,4- and 2,6-xylydine (rats, 4 wk): <ul style="list-style-type: none"> ◦ 500 mg/kg/d dose increased to 700 mg/kg/d after 2 wk ◦ mortality, body weight reduction, decreased Hb concentration and haematocrit and liver cell necrosis at 500–700 mg/kg/d ◦ effects most pronounced in groups exposed to 2,4-xylydine • Fatty liver degeneration, increased liver weight and vomiting at 10 and 50 mg/kg/d of 2,4-, 2,5- and 2,6-xylydine in sub-chronic gavage study (dogs, 4 wk); NOAEL of 2 mg/kg/d; effects were most severe in 2,6-xylydine groups • Liver toxicity (cats) at 17.4 ppm and increased mortality, pneumonitis and degeneration of the heart, liver and kidney cells at 50–142 ppm (rats, guinea pigs, rabbits, cats) reported in sub-chronic inhalation study (7 h/d, 5 d/wk, 10 wk); NOAEC of 7.8 ppm (cats), 17.4 ppm (all other species) • Increased vascular tumours in males at 6,000 ppm, but not at 12,000 ppm, reported in chronic feeding study using 2,5-xylydine (mice, 18 mo) • Non-carcinogenic at 3,000–12,000 ppm in chronic feeding study (male rats, 18 mo) 		

Source	Year set	Standard
<ul style="list-style-type: none"> Equivocal mutagenicity <i>in vitro</i> and <i>in vivo</i>; point mutations observed <i>in vitro</i> in bacteria, inhibition of testicular DNA synthesis <i>in vivo</i> (mice) with 2,3-, 2,6- and 3,5-xylylidine, but not with other isomers at 200 mg/kg oral dose or 100 mg/kg IP dose. <p>Insufficient data to recommend a TLV-STEL or notations for sensitisation.</p>		
DFG	1966	Not assigned
<p>Summary of additional information:</p> <p>MAK not established due to potential genotoxic carcinogenicity. Available data suggests xylylidine isomers are candidates for category 5 carcinogenicity classification (substances for which weak genotoxic carcinogenic properties are observed that may be prevented if a MAK is observed), but there is currently insufficient supporting data on dose-dependence of carcinogenicity and responses in different species.</p> <p>2,4- and 2,6-xylylidine are classified as category 2 carcinogens based on positive carcinogenicity in animals. 2,3-, 2,5-, 3,4- and 3,5-xylylidine are provisionally classified as category 3A carcinogens based on analogy to 2,4- and 2,6-xylylidine.</p> <p>Skin notation recommended based on evidence for systemic effects following dermal absorption in animals.</p> <p>Human data:</p> <ul style="list-style-type: none"> MetHb in patients treated with lidocaine, of which 2,6-xylylidine is a metabolite <p>Animal data:</p> <ul style="list-style-type: none"> Dermal LD₅₀: 1,500 mg/kg (rabbits), 2,000 mg/kg (rats), 1,670 mg/kg (mice): <ul style="list-style-type: none"> dermal LOAEL for signs of toxicity (not specified): 500 mg/kg (mice, rats, rabbits) 5% increased MetHb at 500–2,000 mg/kg dermal dose (dogs) Significant increase in lung tumours at 250 mg/kg/d (females), but not at 125 mg/kg/d in chronic feeding study using 2,4-xylylidine (mice, 18 mo) Increased incidence of nasal cavity adenomas and carcinomas at 150 mg/kg/d of 2,6-xylylidine in progeny of 2-generation chronic feeding study with dose groups 0, 15, 50, 150 mg/kg/d (rats, 2 yr) and increased incidence of subcutaneous fibromas and fibrosarcomas in all exposure groups (statistical significance of incidences not specified) Equivocal genotoxicity <i>in vitro</i> and <i>in vivo</i>; isomers with <i>o</i>-substituents, e.g. 2,3-, 2,4-, 2,5- and 2,6-xylylidine, more mutagenic than other isomers <i>in vitro</i> due to conformation of resulting DNA adduct; 2,6-xylylidine did not produce micronuclei in bone marrow (mice) or recessive lethal mutations (<i>Drosophila melanogaster</i>) <i>in vivo</i>. <p>Insufficient data to recommend a sensitiser notation.</p>		
SCOEL	NA	NA
No report.		
OARS/AIHA	NA	NA
No report.		
HCOTN	2002	Not assigned
<p>Summary of additional information</p> <p>Available report separately assesses carcinogenic risk of individual isomers; no administrative OEL or HBROEL are reported or discussed.</p> <p>2,3-xylylidine</p>		

Source	Year set	Standard
		<ul style="list-style-type: none"> • Non-mutagenic <i>in vitro</i> in bacteria • No other information on genotoxicity or carcinogenicity in animals or humans available • Insufficient evidence to recommend a classification.
		2,4-xylylidine
		<ul style="list-style-type: none"> • No human exposure data available • Increased tumorigenicity in at 250 mg/kg/d in chronic feeding study (mice, 18 mo, also reported in DFG, 2003) not considered in evaluation due to inadequate study design • Limited evidence for mutagenicity <i>in vitro</i> in bacteria and <i>in vivo</i> in mice • Insufficient evidence to recommend a classification.
		2,5-xylylidine
		<ul style="list-style-type: none"> • No human exposure data available • Impairment of DNA repair activity <i>in vitro</i>, no information for <i>in vivo</i> mutagenicity • Insufficient evidence to recommend a classification.
		2,6-xylylidine
		<ul style="list-style-type: none"> • No human exposure data available • Evidence for carcinogenicity at 15–150 mg/kg/d in 2-generation chronic feeding study (rats, also reported in DFG, 2003) • Tumour-promoting effects in nasal cavity at 3,000 ppm of diet in chronic feeding study, tumour induction with single subcutaneous injection of known tumour inducer • Results of genotoxicity assays are equivocal <i>in vitro</i> and <i>in vivo</i> • HCOTN recommends category 2 classification; substance should be regarded as carcinogenic to humans.
		3,4-xylylidine and 3,5 xylylidine
		<ul style="list-style-type: none"> • No data available except for 1 bacterial mutagenicity assay, which was positive in the presence of metabolic activation and 1 briefly reported case of testicular DNA synthesis inhibition at 100 mg/kg/d IP injection of either substance (mice) • Insufficient evidence to recommend a classification.

Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✓ 2015	<ul style="list-style-type: none"> • Grouped assessment of all xylylidine isomers due to structural, physicochemical and toxicological similarities • Substances in group considered genotoxic based on weight of available <i>in vitro</i> and <i>in vivo</i> genotoxicity data: <ul style="list-style-type: none"> ○ haemolysis and methaemoglobinaemia are markers of formation of genotoxic metabolites and are associated with exposure to all isomers • 2,4- and 2,6-xylylidine not sensitising in OECD-compliant sensitisation study (no further details); no sensitisation data available for other isomers.
OECD	✓ 2012	<ul style="list-style-type: none"> • Grouped assessment of all xylylidine isomers due to structural, physicochemical and toxicological similarities • Most general target organ of all isomers is the blood, all isomers cause MetHb formation at 50 mg/kg/d in animals

Source	Year	Additional information
		<p>(species not specified, no further exposure details), 2,4-xylylene caused haematological changes at 10 mg/kg/d:</p> <ul style="list-style-type: none"> ○ papillary necrosis, tubule dilation and hyaline droplets observed in kidneys at 10 mg/kg/d of 2,4-xylylene in OECD 422- and 407-compliant studies (6 mo, no further details) ○ lowest NOAEL for blood, liver and kidney effects is 2 mg/kg/d with corresponding LOAEL of 10 mg/kg/d (no further details) <ul style="list-style-type: none"> • Fatty liver degeneration at 2 mg/kg/d of 2,6-xylylene, but not with the other tested isomers, reported in non-GLP-compliant repeat oral dose study (dogs, 28 d, also reported in ACGIH): <ul style="list-style-type: none"> ○ agency considers 2 mg/kg/d a LOAEL based on toxicity of 2,6-isomer • Agency summarises available animal exposure data • NOAEL of 2–12 mg/kg/d and LOAEL of 10–60 mg/kg/d for adverse haematopoietic, liver and kidney effects • Available studies suggest substances in group are mutagenic <i>in vitro</i> and <i>in vivo</i>.
US NIOSH	✓ 1994	IDLH based on acute toxicity data in animals.

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	<i>All isomers</i> : Carc. Cat 3, Skin
HCIS	2,6-xylylene: Carcinogenicity – category 2 <i>All other isomers</i> : —
NICNAS	2,6-xylylene: Carc. Cat. 3
EU Annex	2,6-xylylene: Carcinogenicity – category 2 <i>All other isomers</i> : —
ECHA	<i>All isomers</i> : Carcinogenicity – category 2
ACGIH	<i>All isomers</i> : Carcinogenicity – A3, Skin
DFG	2,4- and 2,6-xylylene: Carcinogenicity – 2 2,3-, 2,5-, 3,4- and 3,5-xylylene: Carcinogenicity – 3A <i>All isomers</i> : H (skin)



Source	Notations
SCOEL	NA
HCOTN	2,6-xylydine: Carcinogenicity – category 2 All other isomers: —
IARC	2,4- and 2,5-xylydine: 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

Adverse effects in human case study:	
Dermal LD ₅₀ ≤ 1000 mg/kg:	no
Dermal repeat-dose NOAEL ≤ 200 mg/kg:	yes
Dermal LD ₅₀ /Inhalation LD ₅₀ < 10:	
In vivo dermal absorption rate > 10%:	
Estimated dermal exposure at WES > 10%:	yes

consider assigning a skin notation

IDLH

Is there a suitable IDLH value available? Yes

Additional information

Molecular weight:	121.20
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 4.9 mg/m ³ ; 1 mg/m ³ = 0.2 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 checked="" 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 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) (2003) Xylidine (isomers) – 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) (2002) Xylidine (isomers). Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2002/10OSH.

International Agency for Research on Cancer (IARC) (1987) An Updating of IARC Monographs Volumes 1 to 42. Supplement 7.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Xylidines: Human health tier II assessment – IMAP report.

Organisation for Economic Cooperation and Development (OECD) (2012) SIDS initial assessment profile – Dimethylaniline Category.

Tenth Adaptation to Technical Progress Commission Regulation (EU Annex) 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 National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – xylidine.