O-TOLIDINE

CAS number: 119-93-7

Synonyms: 3,3'-Dimethylbenzidine, 3,3'-dimethylbiphenyl-4,4'-biphenyldiamine, 3,3'-dimethylbiphenyl-4,4'-diamine, 4,4'-diamino-3,3'-dimethylbiphenyl

Chemical formula: $C_{14}H_{16}N_2$

Workplace exposure standard (new)

TWA: —

STEL: —

Peak limitation: —

Notations: **Carc. 1B, Sk.**

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

Insufficient data available to recommend a WES. Inhalational and dermal exposure should be minimised as far as possible to protect for respiratory tract irritation and cancer.

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

o-Tolidine is used in the production of dyes and in analytical chemistry.

The critical effects of exposure are respiratory tract irritation and potentially bladder cancer.

The available toxicological database is poor (ACGIH, 2018; DFG, 1993; US EPA, 1991). Acute exposure studies with volunteers demonstrate sneezing spasms and upper respiratory tract irritation following inhalation and rapid skin absorption following dermal application (DFG, 1993). Epidemiological studies indicate likely carcinogenic activity in exposed workers but are confounded by mixed exposures to other structurally related biphenyl amines such as benzidine or dye derivatives. Carcinogenic potential is reported in chronic exposure studies with animals. However, a threshold for this effect is not determined in the available source material. Genotoxicity and clastogenicity are reported *in vitro* and *in vivo*, respectively and are supported by evidence for the formation of genotoxic metabolites from the pure substance or dye product derivatives (ACGIH, 2018; DFG, 1993).

The available data summaries in the primary sources are brief and not detailed. The primary source agencies uniformly suggest that there are insufficient data to recommend a numerical TWA equivalent value (ACGIH, 2018; DFG, 1993). In view of these recommendations, the unconfirmed but likely genotoxic carcinogenicity (NICNAS, 2014) and inadequacy of the available database for determining an inhalational carcinogenic unit risk factor (US EPA, 1991), a WES value that minimises the risk of

cancer cannot be recommended. A further review of the literature is recommended at the next scheduled review

Recommendation for notations

Classified as a category 1B 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.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***Not assigned***
ACGIH	***2001***	***Not assigned***

TLV-TWA not established due to lack of adequate experimental or occupational data.

Summary of information:

Based on structural and toxicological similarity to biphenyl amine, benzidine, carcinogenicity and appreciable skin absorption expected; A3 carcinogenicity and skin notations recommended. Carcinogenicity notation supported by limited epidemiological studies and demonstrated tumorigenicity in animal studies.

Human data:

- Rapidly absorbed through intact human skin (no further details provided)
- Most occupational exposure data are confounded by co-exposure to other biphenyl amines
- Elevated risk of bladder cancer associated with occupational exposure to biphenyl amine mixtures in dye manufacturing
- No evidence for skin irritation from occupational exposure.

Animal data:

- Dose-dependent mortality at >5,000 ppm reported in an acute drinking water study with dose groups 600, 1,250, 2,500, 5,000 and 7,500 ppm of drinking water (rats, 14 d):
  - necrotic hepatocytes, nephropathy and bone marrow depression observed at 2,500 ppm
- Similar observations made in sub-chronic drinking water study with dose groups 300, 500, 1,000, 2,000 and 4,000 ppm of drinking water (rats, 13 wk)
  - reduced thymus weight and lymphocyte atrophy in thymus, spleen and lymph nodes at 1,000–4,000 ppm (no further details provided)
- Mammary carcinomas reported following administration by gavage (rats, no further details provided)
- Dose-related incidence of fatal lung tumours in chronic drinking water study with dose groups 0, 5, 9, 18, 35, 70 and 140 ppm of drinking water (mice, 2 yr, no further details)
- Increased incidence of skin, lung, liver and intestinal tumours in repeat drinking water study with dose groups 0, 30, 70 and 150 ppm (rats, 14 mo)
- Conflicting results reported for *in vitro* mutagenicity assays with bacterial and mammalian cells in the presence or absence of metabolic activation:
  - dyes produced from o-tolidine are converted to genotoxic metabolites in the liver

Insufficient data to recommend a TLV or a sensitiser notation.

DFG	***1993***	***Not assigned***

Summary of additional information:

MAK not established due to sufficient evidence for carcinogenicity in chronic animal studies (also cited in ACGIH, 2018) and likely formation of genotoxic metabolites (Category 2).

Skin notation recommended based on high dermal absorption rate.

Source	Year set	Standard
Human data: • Brief inhalation causes sneezing spasms and irritation of the upper respiratory tract (no further details provided) • Haematuria and kidney tumours reported in production workers exposed to mixtures containing the substance • Urinary excretion of 0.082 mg of a 130 mg dermal dose after 24 h reported in volunteer dermal application study • Urinary excretion of 5.6–7.47 mg/d of 100 mg oral dose over 4 d reported in volunteer oral dose study • Available epidemiological data and results of case studies are conflicting or confounded by mixed exposures to other biphenyl amines and dye derivatives: o no evidence for increased tumorigenicity over 20 yr in workers exposed to mixtures containing substance reported in 1 study o 23 cases of urinary passage cancers in workers exposed to mixtures reported in a separate study; 14 cases involved workers with <6 yr employment • Cited investigation of occupationally induced bladder cancer concludes *o*-tolidine should be treated as a human carcinogen, analogous to benzidine (no further details provided). Animal data: • Rapidly absorbed through skin; dermal penetration increases with temperature and humidity (no further details provided) • Increased tumour incidence (Zymbal's gland) at 10 mg/animal of pure substance or 1:1 mixture with benzidine in chronic subcutaneous injection study (rats, 1 d/wk, 210–225 d) • Mutagenic *in vitro* in bacteria when bacteria preincubated with hydrogen peroxide or in the presence of acetyl coenzyme A and metabolic activation: o *o*-tolidine-based dyes also mutagenic in bacteria in the presence of metabolic activation • Increased SCE in bone marrow cells following IP injection with dose groups 10, 20, 40 and 80 mg/kg (mice).		
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	✓	2014	• Grouped assessment with other benzidine congeners: o These chemicals are all reasonably anticipated to be human carcinogens and have similar uses. • Several animal studies indicate that the chemicals are genotoxic *in vivo* and *in vitro*

Source		Year	Additional information
			• Extensive binding to tissue DNA in liver, bladder and small intestine following single oral dose of structurally related 3,3'-dichlorobenzidine (rats, mice).
US EPA	✓	1991	• Agency determined database to be inadequate for derivation of an inhalation reference dose (RfC).

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	Yes
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	Carcinogenicity – category 1B
NICNAS	Carc. Cat. 2
EU Annex	Carcinogenicity – category 1B
ECHA	Carcinogenicity – category 1B
ACGIH	Carcinogenicity – A3
DFG	Carcinogenicity – 2
SCOEL	NA
HCOTN	NA
IARC	Carcinogenicity – Group 2B
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:	
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:	212.28
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 8.68 mg/m^3; 1 mg/m^3 = 0.12 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) 3,3′-Dimethylbenzidine – 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).

International Agency for Research on Cancer (IARC) (1972) Volume 1, Some inorganic substances, chlorinated hydrocarbons, aromatic amines, n-nitroso compounds, and natural products. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) Benzidine congeners: Human health tier II assessment – IMAP report.

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).