NITROBENZENE

CAS number: 98-95-3

Synonyms: Nitrobenzol

Chemical formula: $C_6H_5NO_2$

Structural formula: —

Workplace exposure standard (retained)

TWA: **1 ppm (5 mg/m^3)**

STEL: **—**

Peak limitation: **—**

Notations: **Carc. 2; 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 1 ppm (5 mg/m^3) is recommended to protect for methemoglobinemia and effects on the spleen in exposed workers.

Discussion and conclusions

Nitrobenzene is used as an intermediate in the preparation of aniline, benzidine and other chemicals. It is also used in the manufacture of cellulose ethers and acetate, in shoe and metal polishes and as a solvent.

Critical effects are methemoglobinemia and effects on the spleen.

A NOAEC of 1 ppm was reported in humans with respect to methaemoglobin formation. Methaemoglobinaemia in workers observed following exposure at 6 ppm (no further information) and in animal inhalation studies at 5 ppm (ACGIH, 2018). Tumourigenicity reported in rats following repetitive long-term inhalations at 5 ppm (ACGIH, 2018 and SCOEL, 2002). No evidence of tumorigenicity provided in humans (ACGIH, 2018; and DFG, 2017). A NOAEC of 1 ppm was reported in rats for formation of methaemoglobin and effects on the spleen (DFG, 2017).

The current TWA of 1 ppm (5 mg/m^3) is recommended to be retained based on the weight of evidence presented, it is considered to protect for methemoglobinemia and effects on the spleen in exposed workers.

Recommendation for notations

Classified as a category 2 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 based on dermal absorption data in humans and animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 1 ppm (5 mg/m^3)***
ACGIH	***2001***	***TLV-TWA: 1 ppm (5 mg/m^3)***

TLV-TWA recommended to minimise the potential for methemoglobinemia.

Summary of data:

No derivation provided; justified by reported NOAEC of 1 ppm in humans.

Human data:

- Study in plant workers exposed at an average of 6 ppm (no further exposure details); 1 or 2 cases of headache or vertigo reported; small amounts of methaemoglobin and sulfhaemoglobin and some Heinz bodies; no further details
- Reported a NOAEC of 1 ppm in humans based on following:
  - Study of metabolite excretion of *p*-nitrophenol in workers; consider 35 mg/d to be the maximum allowable daily dose; controls exposed at 1 to 6 ppm with no ill effects; no further information
  - Study reported that 1 to 5 ppm considered safe level for daily exposure; no further information
- Human volunteers exposed to either 1.0 or 5.5 ppm in air, up to 50% of the absorbed dose could be attributed to percutaneous absorption.

Animal data:

- LD_{50}: 600 mg/kg (rat, oral)
- Topical application of unknown amount on mice killed 12/18 females and 8/10 males
- More pronounced neurotoxicity than IV injection following topical application on rabbits
- Rats and mice exposed at 0, 5, 16, or 50 ppm 6 h/d, 5 d/wk for 90 d; dose related increase in methemoglobin
- Inhalation study 6 h/d, 5 d/wk for 107 wk at 0, 5, 25, or 50 ppm for (mice) or 0, 5, 15, or 25 ppm (rats); increase of nasal inflammatory lesions and the occurrence of methaemoglobinaemia anaemia; increased incidences of alveolar, bronchiolar, thyroid, hepatic, and renal tumorigenicity.

No evidence of genotoxicity.

Insufficient evidence to recommend a SEN notation of TLV-STEL.

DFG	***2017***	***MAK: 0.1 ppm (0.51 mg/m^3)***

MAK recommended to protect for increased methemoglobin formation and systemic effects.

Summary of additional data:

- LOAEL of 9.38 mg/kg/d in rats 90 d gavage dosing study; increase liver weights, decrease in haemoglobin, increase in methaemoglobin; increase kidney weights
- LOAEL of 18.75 mg/kg/d in rats 90 d gavage dosing study; increase liver weights, increase in methaemoglobin; increase reticulocytes
- Extrapolation of LOAEL to airborne concentration:
  - species-specific correction 1:4 rat, 1:7 mouse

Source	Year set	Standard
		○ assumed oral absorption of 100%; inhalation absorption 100% ○ body weight 70 kg ○ respiratory volume 10 m^3 ○ 9.38 mg/kg/d= 16.4 mg/m^3 (3.2 ppm) ○ 18.75 mg/kg/d= 18.8 mg/m^3 (3.7 ppm) • NOAEC of 1 ppm; LOAEC of 5 ppm in rats; 2 yr inhalation; formation of methaemoglobin and minimal effects in spleen; non-adverse pigment deposition in the nasal epithelium at 1 ppm • Basis for MAK: ○ NOAEC of 1 ppm extrapolated to a NOAEC of 0.3 ppm (no derivation) ○ considered same for humans based on effects in spleen more pronounced in rats than humans ○ data from animals therefore halved to 0.15 ppm; preferred value approach rounds down to 0.1 ppm ○ justified as 'far below LOAEL'.
SCOEL	***2002***	***0.2 ppm (0.1 mg/m^3)***
Summary of additional data: • Formation of methaemoglobin in humans and experimental animals after inhalation, oral or percutaneous exposure well established • Methaemoglobinaemia in humans at 6 ppm and in animal inhalation studies at 5 ppm (cited by ACGIH, 2001) • NOAEC of 1 ppm in humans with respect to methaemoglobin formation (cited by ACGIH, 2001) • Tumorigenicity in rats following repetitive long-term inhalations with 5 ppm (cited by ACGIH, 2001) • Justification: a TWA of 0.2 ppm (1 mg/m^3) based on NOAEC of 1 ppm in humans and demonstrated tumorigenicity at 5 ppm in animals; no derivation provided.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✓	• LD_{50}: <300 mg/kg (rabbit, dermal) • No further additional data.

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	—
HCIS	Carcinogenicity – category 2
NICNAS	Carc. Cat. 3
EU Annex	Carcinogenicity – category 2
ECHA	Carcinogenicity – category 1B
ACGIH	Carcinogenicity – A3, Skin
DFG	Carcinogenicity – 4, H (skin)
SCOEL	Skin
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:	
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

IDLH

Is there a suitable IDLH value available?	Yes

Additional information

Molecular weight:	123.11
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m^3; 1 mg/m^3 = 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* on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2017) Nitrobenzene – 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).

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2002) Recommendation from the Scientific Committee on Occupational Exposure Limits for nitrobenzene. SCOEL/SUM/93.

International Agency for Research on Cancer (IARC) (1996) Volume 65, Printing processes and printing inks, carbon black and some nitro compounds. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Benzene, nitro: 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).

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – nitrobenzene.