N-ISOPROPYLANILINE

CAS number: 768-52-5

Synonyms: N-IPA

Chemical formula: $C_9H_{13}N$

Structural formula: —

Workplace exposure standard (interim)

TWA: **0.1 ppm (0.55 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

An interim TWA of 0.1 ppm (0.55 mg/m^3) is recommended to protect for elevated methaemoglobin levels 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

N-isopropylaniline is used as a dye and in chemical synthesis.

The critical effect of exposure is methaemoglobin formation based on evidence from inhalational and dermal studies with animals. The available human and animal exposure data are limited. Methaemoglobin formation is observed above NOAEC of 0.06 and 0.9 ppm in separate sub-chronic inhalation studies with rats (ACGIH, 2018; HCOTN, 2003).

The current recommended occupational exposure levels in the available primary sources documentation are in agreement and appear to be based on analogy to the structurally similar aniline and N,N-dimethylaniline (ACGIH, 2018; HCOTN, 2003). However, a NOAEC of 0.9 ppm for elevated methaemoglobin levels in a sub-chronic inhalation study with rats has been used to derive a health-based recommended OEL (HBROEL) of 0.1 ppm to protect for this endpoint (HCOTN, 2003).

In view of the uncertainty in the derivations of the TWA equivalents reported by ACGIH (2018) and HCOTN (2003) and the HBROEL proposed by HCOTN (2003), an interim TWA of 0.1 ppm (0.55 mg/m^3) is recommended to protect for methaemoglobin formation. Further assessment of additional source material, regarding methaemoglobin formation in humans and the suitability of analogies to other structurally related anilines, is recommended during the next scheduled review.

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 based on evidence for potential dermal absorption and adverse systemic effects in animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 2 ppm (11 mg/m^3)***
ACGIH	***2001***	***TLV-TWA: 2 ppm (11 mg/m^3)***

TLV-TWA intended to minimise the potential for methaemoglobinaemia formation. TLV-TWA based on structurally and toxicologically related aromatic amines, aniline and N,N-dimethylaniline. By this analogy, a skin notation is warranted. A BEI for methaemoglobin levels is recommended.
Summary of data:
Human data:
• Aromatic amines, including N-isopropylaniline, cause methaemoglobinaemia from oral, dermal and inhalational exposure (no further details provided).
Animal data:
• Oral LD_{50}: 560 mg/kg (rats); oral LD_{50} comparable to aniline (440 mg/kg, rats)
• LD_{50}: 3,550 mg/kg (rabbits, dermal); slight eye and skin irritant
• LC_{50}: 218 ppm (rats, 4 h); CNS depression and body weight reduction
• Sub-chronic inhalation study with treatment groups 0.9, 3.6, and 18 ppm (rats, 6 h/d, 5 d/wk, 14 wk) reported:
  ○ decreased body weight gain, increased spleen and kidney weight, and haemosiderosis in spleens of 18 ppm group
  ○ dose-dependent increase in methaemoglobin in all groups
• No foetal or embryonic toxicity at 30 or 100 mg/kg/d in repeat gavage developmental study (unspecified species, GD 6–15); malformations observed at overtly maternally toxic levels (unspecified)
• Non-mutagenic *in vitro* in bacteria and yeast
• Carcinogenic potential not discussed.
 	
Insufficient data available to recommend a STEL or notations for carcinogenicity or sensitisation.		

DFG	***NA***	***NA***
No report.		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2003***	***TWA: 2 ppm (10 mg/m^3)***
Summary of additional data: Current administrative level considered too high following health-based risk assessment. Methaemoglobin formation considered the critical effect. 14-wk inhalation study with rats (also cited in ACGIH, 2018) used in derivation of HBROEL. Methaemoglobin levels (1.4%) at 0.9 ppm were the		

Source	Year set	Standard

same as those at 5.6 ppm in a 2 wk study, but not considered toxicologically relevant to workplace exposure regarding a BEI of 1.5% set by the ACGIH for methaemoglobin blood concentrations.
An HBROEL of 0.1 ppm as an 8 h TWA is obtained using the NOAEL of 0.9 ppm and applying an overall factor of 9 to account for inter- and intraspecies differences. A skin notation is currently recommended, but is not supported by a health-based assessment due to lack of quantitative absorption data.
Animal data:
• 70% of 15 mg/kg ip dose excreted in urine after 24 h (rats); 80–90% after 96 h
• Eye irritation in rabbits was reversible within 7 d
• Non-sensitising in patch test with 0.3 mL undiluted substance (guinea pigs, 1/wk, 3 wk, challenged 14 d after last dose)
• Anaemia and methaemoglobinaemia at 100 and 400 mg/kg/d in repeat dermal application study (rats, neat, non-occlusive, 6 h/d, 5 d/wk, 1 mo); interferences in analytical methods complicate interpretation of results
• Lachrymation and hypoactivity at 89 ppm, and dose-dependent frequency of nasal discharges and encrustation in treatment range 10–89 ppm (rats, 6 h/d, 5 d/wk, 4 wk)
• Sub-chronic inhalation study with exposure groups 0.06, 0.5, 5.6 ppm (rats, 6 h/d, 5 d/wk, 2 wk) reported:
  ○ no histopathological changes noted
  ○ elevated methaemoglobin levels ≥0.5 ppm
• No effects on female fertility at 3.6 ppm or male fertility at 18 ppm in repeat inhalation study (rats, 11 wk); lower rate of pregnancy at 18 ppm, but no changes in outcome
• Non-mutagenic *in vitro* or *in vivo*.
 	
Insufficient data to assess carcinogenicity.		

Secondary source reports relied upon

Source		Year	Additional information
ECHA	✓	2019	• Not yet assessed; predicted as likely to meet criteria for category 1A or 1B carcinogenicity, mutagenicity, or reproductive toxicity.

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	NA
NICNAS	NA

Source	Notations
EU Annex	NA
ECHA	—
ACGIH	Skin
DFG	NA
SCOEL	NA
HCOTN	Skin
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:	no	
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%:	no	
		a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	135.21
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 5.52 mg/m^3; 1 mg/m^3 = 0.181 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.

European Chemicals Agency (ECHA) (2019) N-isopropylaniline – REACH assessment.

Health Council of the Netherlands (HCOTN) (2003) N-Isopropylaniline. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/083.