P-NITROANILINE

CAS number: 100-01-6

Synonyms: 1-Amino-4-nitrobenzene, 4-nitroaniline, azoic diazo component 37 (C.I. 37035), developer 17, benzeneamine,4-nitro

Chemical formula: $C_6H_6N_2O_2$

Structural formula: —

Workplace exposure standard (retained)

TWA: **3 mg/m^3**

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **300 mg/m^3**

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 3 mg/m^3 is recommended to protect for elevated blood methaemoglobin and liver effects in exposed workers.

Discussion and conclusions

p-Nitroaniline is used in the preparation of dyes, the manufacture of antioxidants, gasoline gum inhibitors and poultry medicines.

Critical effects of exposure include methaemoglobinaemia and liver effects.

No quantitative human exposure data are available. Human data available is only from accidental poisonings, with a report of death of an individual who was already afflicted with liver disease. Other individuals from same incident became cyanotic with reports of headache, sleepiness, weakness and respiratory distress. Exposure concentrations are not known (ACGIH, 2018). A NOAEL of 0.25 mg/kg/day in rats is reported for effects on the spleen in a chronic gavage study (ACGIH, 2018). ACGIH (2018) and DFG (1999) reported a LOAEC of 10 mg/m^3 for effects on spleen in a four-week rat inhalation study. From this same study, NICNAS (2017) and NTP (1993) reported a LOAEC of 5 mg/m^3. This discrepancy in LOAEC by primary and secondary sources indicates an error in reporting doses. These reported LOAEC from the four-week inhalation study do not fit with NOAEL reported from chronic gavage study. It is difficult to compare between species because biological activity of *p*-nitroaniline is expected to be dependent on exposure route and dose (DFG, 1999). Because of this, a NOAEC in humans could not be determined from available animal data to derive an occupational exposure limit.

p-Nitroaniline is considered a more potent cyanogenic and anaemiagenic than aniline. Both ACGIH (2018) and DFG (1999) considered that the occupational exposure limit of *p*-nitroaniline should be

below aniline (ACGIH TLV-TWA of 7.6 mg/m^3). ACGIH and SWA are the only primary agencies that recommend occupational exposure limit for *p*-nitroaniline. Note SWA TWA for aniline and homologous is recommended to change from 7.6 mg/m^3 to 0.5 mg/m^3 based on a health-based risk assessment. However, no data are available to support a change in TWA for *p*-nitroaniline.

In absence of any other available data, the TWA of 3 mg/m^3 by SWA and ACGIH (2018) is recommended and supported by US NIOSH (1994) evaluation. The recommended TWA is considered to protect for potential anaemia, cyanosis, tissue anoxia and liver effects in exposed workers.

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 review of dermal sensitisation is recommended at the next review as there appears to be enough evidence to warrant a notation (NICNAS, 2017).

A skin notation is recommended based on evidence of dermal absorption and adverse systemic effects in animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 3 mg/m³***
Established based on ACGIH recommendation.		
ACGIH	***2001***	***TLV-TWA: 3 mg/m³***

TLV-TWA recommended to minimise potential for anaemia, cyanosis and tissue anoxia in exposed workers as well as effects on the liver.

No specific derivation of TLV-TWA explained but mentioned:

- p-Nitroaniline more potent cyanogenic and anaemiagenic than aniline
- Particulate or mist exposure at elevated temperatures are hazardous
- Accordingly, established TLV-TWA below aniline (TLV-TWA of 7.6 mg/m^3).

Summary of data:

Human data:

- Potent inducer of methaemoglobin and haemolysis can occur at high or prolonged exposures
- Readily absorbed through skin and may cause corneal damage
- Reports of poisoning among workers who swept up the powder in the hold of a ship; one death following jaundice in man already afflicted with liver disease; others became cyanotic with reports of headache, sleepiness, weakness and respiratory distress
- Recommendation for the TLV to be expressed in mg/m^3 rather than ppm given that the steam-borne mists, rather than ambient vapours, caused cyanogenic and anaemiagenic effects
- Found in samples of red wax crayons and para-red dye and inferred to be responsible for poisoning of children who ate red wax crayons.

Animal data:

- No mortality or reduction in body weight in rats inhaling 0, 10, 30 or 90 mg/m^3 (6 h/d, 5 d/wk for 4 wk):
  - a dose-related increase in circulating MetHb
  - decrease in erythrocyte counts, haematocrit values and haemoglobin concentrations at all concentrations
  - key lesions in spleen were extramedullary haematopoiesis and hemosiderosis
  - higher degree of extramedullary haematopoiesis in females at 90 mg/m^3 in comparison to controls
- Doses of 10, 30, 100 and 300 mg/kg/d by oral gavage for 14 d in mice caused significant increase in methaemoglobin:
  - administration of 1,000 mg/kg/d caused 100% mortality by day 4
  - doses of 30–300 mg/kg/d caused significant reduction in erythrocyte counts
- No deaths reported in a 13-wk study of mice administered 0, 1, 3, 10, 30 or 100 mg/kg/d by gavage caused:
  - similar haematologic findings to those of the 14-d study
- A statistically significant increases in methaemoglobin and decreased erythrocyte counts at 1.5 and 9 mg/kg/d in a chronic study in rats (2 yr) administered 0, 0.25, 1.5 or 9 mg/kg/d by oral gavage. No increase in tumours or splenic fibrosarcomas reported

Source	Year set	Standard
• NTP concluded equivocal evidence of carcinogenicity in male mice: o intubation of 30 or 100 mg/kg/d (duration not stated) in male mice caused increased incidence of hepatic haemangiosarcomas and increased incidence of haemangioma or hemangiosarcoma (combined) at all sites o no evidence of carcinogenicity in female mice at any dose • Negative results in genotoxic assays. Insufficient data available to recommend sensitiser notation or TLV-STEL.		
DFG	***1999***	***Not assigned***
Summary of additional data: • No useful human exposure data available • 24 h following application (in acetone) to isolated human skin *in vitro*, 34.5% absorption and 100% absorption *in vivo* applied to shaved abdominal skin of monkeys • LD_{50}: 810 mg/kg (mice, oral); 750–3,250 mg/kg (rats, oral) • Negative for allergenic effects in guinea pigs • Insufficient data to derive MAK because: o 10 mg/m^3 produced effects in the spleen in a 4-wk inhalation study in rats (cited in ACGIH, 2018) o 0.25 mg/kg/d caused effects in the spleen in a chronic toxicity study in rats by gavage (cited in ACGIH, 2018) o biological activity expected to be highly dependent on exposure route and dose, making species comparisons difficult o however, previous MAK of 5.7 mg/m^3 is too high and should be well below MAK for aniline (7.7 mg/m^3).		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2008***	***Not assigned***
Summary of additional data: • Evaluation of the carcinogenicity and genotoxicity • Carcinogenic mechanism which caused tumours in male mice unclear • Committee noted p-nitroaniline had not been sufficiently investigated. While available data does not warrant classification as carcinogenic to humans, it was recommended to classify as *a suspected human carcinogen*.		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2017	• LD_{50}: >500 mg/kg (guinea pigs, dermal) • Not found to be irritating to skin of rabbit • Considered a skin sensitiser and warrants a hazard classification • Rats exposed at 0, 5, 15 or 45 mg/m^3 (6 h/d, 5 d/wk for 4 wk): o increase in mean spleen weights - referenced NTP document for *Nair et. al, 1986* study • Insufficient evidence to evaluate genotoxicity potential.
NTP	✓	1993	• Evaluated *Nair et. al 1986* cited by ACGIH (2001): o exposure concentrations as mentioned by NICNAS o mean spleen weights increased in all dose group, only reported lesions were hemosiderosis and haematopoiesis.
US NIOSH	✓	1994	• REL=3 mg/m^3 • IDLH based on analogy to aniline.

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	—
HCIS	NA
NICNAS	NA
EU Annex	NA
ECHA	NA
ACGIH	Carcinogenicity – A4, Skin
DFG	Carcinogenicity – 3A, H (skin)
SCOEL	NA
HCOTN	—
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:	
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%:	yes
Estimated dermal exposure at WES >10%:	
	consider assigning a skin notation

IDLH

Is there a suitable IDLH value available?	Yes

Additional information

Molecular weight:	138.12
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) (1999) 4-Nitroaniline – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2008) p-Nitroaniline. Evaluation of the carcinogenicity and genotoxicity. The Hague: Health Council of the Netherlands; publication no. 2008/08OSH.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2017) Benzenamine, 4-nitro-: Human health tier II assessment – IMAP report.

National Toxicology Program (NTP) (1993) NTP Technical Report on the Toxicology and Carcinogenesis Studies of p-Nitroaniline (CAS NO. 100-01-6) in $B6C3F_1$ Mice (Gavage Studies).

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