PHENYLHYDRAZINE

CAS number: 100-63-0

Synonyms: Hydrazinobenzene

Chemical formula: $C_6H_8N_2$

Structural formula: —

Workplace exposure standard (retained)

TWA: **0.1 ppm (0.44 mg/m^3)**

STEL: **—**

Peak limitation: **—**

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

IDLH: **15 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 0.1 ppm (0.44 mg/m^3) is recommended to protect for irritation of the skin and nose, dermatitis and skin sensitisation in exposed workers.

Discussion and conclusions

Phenylhydrazine is used in the synthesis of dyes and pharmaceuticals and as a reagent in chemical analysis. Its clinical application was in the treatment of *polycythaemia vera*. However, due to its toxicity, this use has ceased (ACGIH, 2018).

Critical effects of exposure include haemolytic anaemia, dermatitis and skin hypersensitivity (ACGIH, 2018; ECHA, 2019).

Very limited toxicological human data is available. Mutagenicity is demonstrated in *in vivo* and *in vitro* studies and increased incidence of tumours in the lung and blood vessels occurred in mice. However, DFG (1998) highlight inadequacies in these carcinogenicity studies, hence considered unreliable.

A NOAEC of 0.12 mg/m^3 reported from a six-month rat study; however, this study was incompletely documented (DFG, 1998). Whilst the derivation of the TLV-TWA recommended by ACGIH (2018) is not provided, a TWA of 0.1 ppm is recommended be retained to limit irritant effects and possible sensitisation.

Recommendation for notations

Classified as a category 1B carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser and not a respiratory sensitiser according to the GHS.

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

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1995***	***TWA: 0.1 ppm (0.44 mg/m^3)***
ACGIH	***2001***	***TLV-TWA: 0.1 ppm (0.44 mg/m^3)***

TLV-TWA recommended to minimise the potential for nasal and dermal irritation, dermatitis and skin sensitisation.

Summary of data:

Human data:

- Historically used to treat *polycythaemia vera*; no longer used clinically due to toxicity
- Dermal and inhalation exposure caused haemolytic anaemia, dermatitis and skin hypersensitivity.

Animal data:

- Oral LD_{50}: 200–250 mg/kg (dogs); 188 mg/kg (rats); 175 mg/kg (mice); 80 mg/kg (rabbits and guinea pigs)
- Acute effects: neurologic toxicity, cyanosis, hypothermia, haematuria, vomiting, convulsions and degeneration in liver and kidneys
- Erythema and sloughing of skin at treatment site following dermal exposure in guinea pigs
- Dermal application of 0.1% in Vaseline in rats (every other day for 4 wk) caused weight loss, build-up of squamous epithelium and leukocyte infiltration
- Mice administered 1 mg/d (7 d/wk, 42 wk) showed increased incidence of malignant lung tumours:
  - mice given 0.5 mg (orally) in first 5 wk, then 0.25 mg for 35 wk (5 d/wk), did not show significant carcinogenic response
- 0.01% of the hydrochloride salt in drinking water (0.63–0.81 mg/d) caused increased incidence of blood vessel tumours in mice
- Proposed mechanism of action for carcinogenicity includes indirect alkylation of DNA
- IP injection (10 or 20 mg/kg) to pregnant mice (GD 17–19) resulted in severe jaundice and anaemia in offspring
- Mutagenic in *in vivo* and *in vitro* studies.

Skin notation assigned. Insufficient data to recommend a SEN notation or TLV-STEL.

DFG	***1998***	***Not assigned***

Summary of additional data:

- Acute exposures in humans results in methaemoglobin formation
- Oral administration of 30 mg/d (0.4 mg/kg bw) for 8 d in volunteers caused haemolysis of transfused erythrocytes at a level of 0–10%
- Contact eczema demonstrated in exposed workers
- LC_{50}: 2,120–2,610 mg/m^3 (mouse and rat, inhalation, duration not stated)
- LD_{50}: 500 mg/kg (rabbit, dermal)

Source	Year set	Standard
• Haematological parameters affected in inhalation study of rats at 1.5 mg/m^3 for 3–4 mo; effects reversible within 6 mo • NOEC of 0.12 mg/m^3 reported for 6 mo study of rats; no further information; authors note due to lack of information study is difficult to evaluate • Carcinogenicity studies do not meet current standards (dose-dependency not investigated and only mice used) • Due to evidence of genotoxic effects, MAK withdrawn.		
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	• 6 mo inhalation study with rats, mice, guinea pigs and rabbits, exposed at 15.8 or 22.5 mg/m^3 showed reduced erythrocyte counts and haemoglobin concentrations and increased reticulocyte and methaemoglobinemia (reversible at 15.8 mg/m^3).
ECHA	✓	2019	• Systemic toxicity developed including RBC damage following dermal exposure of liquid phenylhydrazine in humans; no such systemic effects following 2 cases of dermal exposure with solid phenylhydrazine hydrochloride • Based on 3 studies, teratogenicity inconclusive.
US NIOSH	✓	1994	• REL =0.14 ppm (0.6 mg/m^3) 2 h ceiling; PEL =5 ppm (22 mg/m^3) • Considered potential occupational carcinogen • IDLH =15 ppm based on acute oral toxicity animal data in the absence of inhalation data.

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	—
HCIS	Carcinogenicity – category 1B, Skin sensitisation – category 1
NICNAS	Carc. Cat. 2, Skin sensitisation
EU Annex	Carcinogenicity – category 1B, Skin sensitisation – category 1
ECHA	Carcinogenicity – category 1B
ACGIH	Carcinogenicity – A3, Skin
DFG	Carcinogenicity – 3B, H (skin), Sh (dermal sensitiser)
SCOEL	NA
HCOTN	NA
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:	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%:	
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	Yes

Additional information

Molecular weight:	108.14
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) (1998) Phenylhydrazine – 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).

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) Phenylhydrazine and its monohydrochloride: 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 – phenylhydrazine.