HEXAHYDROPHTHALIC ANHYDRIDE

CAS number: 85-42-7

Synonyms: 1,2-Cyclohexanedicarboxylic acid anhydride, cyclohexane-1,2-dicaboxylic anhydride, cis and trans mixture, HHPA, HHPAA, hexahydrophthalic acid anhydride, hexahydro-1,3-isobenzofurandione

Chemical formula: $C_8H_{10}O_3$

Workplace exposure standard (new)

TWA: —

STEL: —

Peak limitation: **0.005 mg/m^3 (inhalable fraction)**

Notations: **DSEN, RSEN**

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

A peak limitation of 0.005 mg/m^3 (inhalable fraction) is recommended to protect for respiratory sensitisation and irritant effects in exposed workers.

Discussion and conclusions

Hexahydrophthalic anhydride (HHPA) is primarily used as a hardener in epoxy resin systems.

HHPA is a known respiratory sensitiser. The critical effects of exposure include asthma, allergic rhinitis and eye and upper respiratory tract irritation. Sensitisation is observed in workers exposed at 10 to 50 µg/m^3. Workers exposed to less than 10 µg/m^3 but with intermittent peak exposures above 50 µg/m^3 (five minutes per week to fifteen minutes per day) had significantly higher levels of specific immunoglobin antibodies compared to others similarly exposed but without the peak exposures (ACGIH, 2018; HCOTN, 2010).

Given that the evidence demonstrates the potential for a severe health effect resulting from acute fluctuations in airborne concentration, a peak limitation of 0.005 mg/m^3 is recommended as derived by ACGIH (2018). This concentration is cited as protective of sensitisation in exposed workers (ACGIH, 2018).

Recommendation for notations

Not classified as a 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 not recommended based on the available evidence.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***NA***	***NA***
No report		
ACGIH	***2015***	***TLV-Ceiling: 0.005 mg/m³ (inhalable fraction and vapour)***
TLV-Ceiling recommended to minimise sensitisation of workers from peak occupational exposures even when otherwise exposed at low concentrations. Summary of data: TLV-Ceiling for all isomers. Human data: • Hapten that binds to endogenous proteins in the lung forming an antigen • Causes immunologic respiratory disease in humans; IgE and IgG-mediated diseases; including sensitisation, asthma, allergic rhinitis, haemorrhagic rhinitis, hypersensitivity pneumonitis, and ocular and upper respiratory tract irritation • Exposure at lower mean levels with occasional peak exposure resulted in the development of the presence of specific IgE or IgG to an HHPA-human serum albumin (HSA) conjugate • TWA exposures >50 µg/m³ in workers resulted in significant increase in levels of specific IgE and IgG antibodies to HHPA-HAS • Workers exposed at <10 µg/m³ with intermittent peak exposures >50 µg/m³ (5 min/wk to 15 min/d) had significantly higher levels of specific IgE antibodies than workers similarly exposed without the peak exposures: o no significant difference between workers with mean exposure of 10 µg/m³ without the peaks and the control group without exposure • Study of mixed exposure HHPA and isomer methylhexahydrophthalic anhydride (MHHPA): o total organic acid anhydride exposure levels of <10 µg/m³ resulted in HHPA sensitisation as indicated by skin-prick test o exposure appeared to be TWA, major peak exposures was not determined. Animal data: • No deaths over 24 h in rabbits dosed with dermal application of 2,000 mg/kg to abraded skin • Corrosive based on Draize test; 6 rabbits with 100 mg of undiluted HHPA without irrigation and with irrigation of the eyes at 30 sec; irrigation after 4 sec resulted in severe but reversible irritation • Positive response for sensitisation in animals. No carcinogenicity data; negative mutagenicity *in vitro*.		
DFG	***1995***	***Not assigned***
No further information.		
SCOEL	***NA***	***NA***
No report.		

Source	Year set	Standard
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2010***	***Not assigned***

Summary of additional data:

- Evaluation of 14 cyclic acid anhydrides including HHPA
- Sites critical effects as irritation of mucous membranes of the eyes and airways and sensitisation-induced work-related diseases
- Sensitisation in workers exposed to HHPA levels of 10–50 µg/m^3
- Allergic contact dermatitis not likely
- Calculated sensitisation risk in workers:
  - TWA of 0.007 µg/m^3 corresponds to an additional risk of 0.1% due to occupational exposure
  - TWA of 0.07 µg/m^3 corresponds to an additional risk of 1% due to occupational exposure
- Additional risks are additional to those caused by occupational exposure on top of the risk of getting sensitised to HHPA in the general population.

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2016	• Complaint of nasal pain and rhinorrhoea in 1 worker following exposure to MHHPA • Evidence of respiratory sensitisation in workers; same evidence as primary sources • Critical health effect is respiratory sensitisation • A skin sensitiser and severely irritating to the eyes • Could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalational exposure are implemented • Low acute toxicity all routes in animals.

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	NA
HCIS	Skin sensitisation – category 1 Respiratory sensitisation – category 1

Source	Notations
NICNAS	NA
EU Annex	Skin sensitisation – category 1 Respiratory sensitisation – category 1
ECHA	NA
ACGIH	RSEN
DFG	Sa (respiratory 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:	no
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%:	
	a skin notation is not warranted

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	154.17
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) (1995) Hexahydrophthalic anhydride/Methyltetrahydrophthalic anhydride – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2010) Cyclic acid anhydrides. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands; publication no. 2010/02OSH.

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).