# 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: | C8H10O3 |

 Workplace exposure standard (new)

| TWA: | **—** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **0.005 mg/m3 (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/m3 (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/m3. Workers exposed to less than 10 µg/m3 but with intermittent peak exposures above 50 µg/m3 (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/m3 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:
* 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):
* total organic acid anhydride exposure levels of <10 µg/m3 resulted in HHPA sensitisation as indicated by skin-prick test
* 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. |
| 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/m3
* Allergic contact dermatitis not likely
* Calculated sensitisation risk in workers:
* TWA of 0.007 µg/m3 corresponds to an additional risk of 0.1% due to occupational exposure
* TWA of 0.07 µg/m3 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.
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### 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.
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### 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 1Respiratory sensitisation – category 1 |
| NICNAS | NA  |
| EU Annex | Skin sensitisation – category 1Respiratory 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 LD50 ≤1000 mg/kg: | no |   |   |
| Dermal repeat-dose NOAEL ≤200 mg/kg: |   |   |   |
| Dermal LD50/Inhalation LD50 <10: |   |   |   |
| *In vivo* dermal absorption rate >10%: |   |   |   |
| Estimated dermal exposure at WES >10%: |   |   |   |
|   |   |   | **a skin notation is not warranted** |

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### 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/m3; 1 mg/m3 = 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*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) 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).