# Piperazine and salts

| CAS number: | 110-85-0  142-64-3 (hydrochloride salt) |
| --- | --- |
| Synonyms: | 1,4-Piperazine, 1,4-diazacyclohexane, diethyleneaiamine, hexahydropyrazine, piperazidne |
| Chemical formula: | C4H10N2  C4H10N2.HCl (hydrochloride salt) |
| Structural formula: | — |

Workplace exposure standard (amended)

| TWA: | **0.03 ppm (0.1 mg/m3)** |
| --- | --- |
| STEL: | **0.09 ppm (0.3 mg/m3)** |
| Peak limitation: | **—** |
| Notations: | **Sk., DSEN, RSEN** |
| IDLH: | **—** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.03 ppm (0.1 mg/m3) is recommended to minimise the potential for occupational asthma, respiratory sensitisation and chronic bronchitis in exposed workers.

A STEL of 0.09 ppm (0.3 mg/m3) is recommended to protect for asthmatic responses in sensitised workers.

## Discussion and conclusions

Piperazine and its salts are used in veterinary products (worm treatment), as a stabiliser in therapeutic products and as an absorbent for carbon dioxide in research. It is also used in the manufacturing of fibres and polymers to manufacture plastics and resins.

Critical effects of exposure are respiratory and skin sensitisation and asthma.

Piperazine and its salts are dermal and respiratory sensitisers. Exposures at or above 0.7 mg/m3 are associated with respiratory symptoms such as dyspnoea, wheezing and coughing in humans. Exposures at 0.4 mg/m3 and 0.1 mg/m3 are not considered to cause respiratory symptoms. Exposure at 0.3 mg/m3 elicits asthma in sensitised workers. Acute exposures result in mild to moderate skin burns and sensitisation in humans. Chronic exposure is found to induce chronic bronchitis in workers. Piperazine solution produces effects on the cornea in rabbits and mild sensitisation in the guinea pig maximisation test (ACGIH, 2018).

Based on the evidence presented in humans, particularly that 0.1 mg/m3 is associated with no observed effects and 0.3 mg/m3 provoked asthma in sensitised individuals, a TWA of 0.03 ppm (0.1 mg/m3) is recommended as derived by the ACGIH (2018). This TWA is cited to minimise the potential for occupational asthma, respiratory sensitisation and chronic bronchitis. A STEL of 0.09 ppm (0.3 mg/m3) (SCOEL, 1997) is also recommended to limit exposures that could result in asthmatic responses in sensitised individuals.

## 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 respiratory sensitiser according to the GHS.

A skin notation is recommended based on systemic effects in humans following dermal exposure.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 5 mg/m3 (piperazine dihydrochloride) | |
| Adopted from ACGIH in 1991 (CAS 142-64-3).  ACGIH merged with Piperazine salts in 2012 (CAS 110-85-0). |
| ACGIH 2014 TLV-TWA: 0.03 ppm (0.1 mg/m3) |
| TLV-TWA recommended to reduce the potential for occupational asthma and respiratory sensitisation and to protect against chronic bronchitis. May not protect sensitised workers.  Summary of data:  Human data:   * Acute exposures caused mild to moderate skin burns and sensitisation * Application to skin (25% aqueous solution) for up to 48 h caused primary dermal irritation with erythema and marked vesiculation in 10/12 volunteers * A 3.2% positive allergic reactions reported in a patch testing of 1% piperazine solution on 93 patients * TLV-TWA based on evidence summarised from several occupational studies demonstrating exposures >0.7 mg/m3 were associated with respiratory symptoms in humans; exposures of 0.4 mg/m3 and 0.1 mg/m3 were not associated with respiratory symptoms in humans; exposure at 0.3 mg/m3 elicited asthma in sensitised workers: * delayed type asthmatic reactions with typical symptoms of dyspnoea, wheezing and coughing * lag time of 1 mo–1 yr between initial exposure and onset of asthma * appears to be information summary from up to 6 different studies * duration or frequency of exposures not provided * no further details * A study of 602 workers involved in piperazine production and processing 1942 –1979 reported overall prevalence of bronchitis at ≈16% * A case-control study conducted within a retrospective cohort of 664 workers exposed to piperazine and other chemicals did not reveal any significant association with any specific chemical and cancer.   Animal data:   * LD50: 4 g/kg (rabbits, dermal) * An aqueous solution containing 1–5% piperazine caused etching and necrosis of the rabbit cornea; rated as a grade 9 on a scale ranging from 1–10; necrosis covering 60–90% of the cornea * Mild sensitiser in a guinea pig maximisation test * Not genotoxic and the limited cancer studies indicate not carcinogenic.   Insufficient data to recommend a TLV-STEL. |
| DFG 1998 Not assigned |
| Available data on the allergic potency of piperazine are not adequate for the establishment of a MAK value.  Summary of additional data:   * Since piperazine has been used medically, the available data as to its effects in humans indicate that neither acute nor chronic toxic effects need be expected after workplace exposures to metal-working fluids * Supplement (2001): insufficient data available to establish MAK based on sensitisation * No additional data. |
| SCOEL 1997 TWA: 0.1 mg/m3; STEL: 0.3 mg/m3 |
| Summary of additional data:   * TWA and STEL based on studies demonstrating no new cases of asthma reported in workers exposed at levels below 0.3 mg/m3 (cited by ACGIH, 2018) * No specific derivation provided. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN NA NA |
| No report. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2018  2019 | * Multiple cases of allergic dermatitis caused by piperazine in therapeutic products reported * Study of 130 workers involved in manufacturing: * asthma associated with occupational exposure identified in 15 current employees and 18 former employees * 29/33 cases of asthma directly related to piperazine * no subjects had a history of asthma before employment * Moderate to severe erythema in rabbits exposed to 0.5 mL as occlusive patches, for 3 min or 1 h. |

### 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 | Respiratory sensitisation – category 1, Skin sensitisation – category 1 |
| NICNAS | — |
| EU Annex | NA |
| ECHA | Resp. Sens. 1, Skin Sens. 1 |
| ACGIH | RSEN, DSEN, Carcinogenicity – A4 |
| DFG | Sa (respiratory sensitiser), Sh (dermal sensitiser) |
| SCOEL | — |
| 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 | 4.00 |  | | Dermal LD50 ≤1000 mg/kg: |  |  |  | | 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 warranted** | |

### IDLH

| Is there a suitable IDLH value available? | No |
| --- | --- |

## Additional information

| Molecular weight: | 86.13 |
| --- | --- |
| 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) (1998) Piperazine – MAK value documentation.

European Chemicals Agency (ECHA) (2019) Piperazine – REACH assessment.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (1997) Recommendation from the Scientific Committee on Occupational Exposure Limits for piperazine. SCOEL/SUM/78.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2018) Piperazine salts: Human health tier II assessment – IMAP report.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2019) Piperazine: Human health tier II assessment – IMAP report.