

## CYCLOHEXYLAMINE

**CAS number:** 108-91-8

**Synonyms:** Aminocyclohexane, cyclohexanamine, hexahydroaniline

**Chemical formula:** C<sub>6</sub>H<sub>13</sub>N

**Structural formula:** —

### Workplace exposure standard (amended)

**TWA:** 2 ppm (8.2 mg/m<sup>3</sup>)

**STEL:** —

**Peak limitation:** —

**Notations:** Sk.

**IDLH:** —

### Sampling and analysis:

### Recommendation and basis for workplace exposure standard

A TWA of 2 ppm (8.2 mg/m<sup>3</sup>) is recommended to protect for acute irritation of the eyes and upper respiratory tract and potential reproductive toxicity in exposed workers.

### Discussion and conclusions

Cyclohexylamine is used as a corrosion inhibitor in cooling water feeds and in the chemical manufacture of insecticides, plasticisers, dry-cleaning soaps and dyes.

Critical effects of exposure are irritation of the eyes and upper respiratory tract due to its corrosive properties. It also causes nausea and vomiting at higher concentrations (ACGIH, 2018).

A NOAEL of 4 ppm for eye and nose irritation is reported in humans following acute exposure, with the LOAEL reported at 10 ppm (DFG, 2017). Chronic inhalation exposure data for humans and animals are limited. Adverse reproductive effects have been reported following chronic exposures in rats in a feeding study with a NOAEL of 15 mg/kg reported (ACGIH, 2018; DFG, 2003).

The recommended TWA of 2 ppm is derived from the NOAEL of 4 ppm for acute exposure in humans and applying a factor of two to account for the local irritation effects reported at the LOAEL. Exposure at the TWA over an eight hour shift equates to a daily intake of approximately 1.2 mg/kg (assuming a 70 kg worker, 10 m<sup>3</sup> respiratory volume and 100% absorption), which is more than 10 times lower than the reported NOAEL of 15 mg/kg for reproductive effects in animals. The TWA is also expected to protect for possible reproductive effects reported in animal studies.

### 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 skin notation has been recommended based on evidence suggesting potential dermal absorption and adverse systemic effects in animals.

Data from animal studies suggest that systemic toxicity may result from dermal absorption. However, it is unclear if the reported toxicity is due to the inherent corrosive nature of the substance. A priority review of available data is therefore recommended during the next scheduled assessment to confirm the requirement for a skin notation.

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# APPENDIX

## Primary sources with reports

Source	Year set	Standard
<b>SWA</b>	<b>1991</b>	<b>TWA: 10 ppm (41 mg/m<sup>3</sup>)</b>
<b>ACGIH</b>	<b>2001</b>	<b>TLV-TWA: 10 ppm (41 mg/m<sup>3</sup>)</b>
<p>TLV-TWA intended to minimise potential for irritation to respiratory tract, skin and eyes, nausea and vomiting. Not classifiable as a human carcinogen based on negative results in animal studies. Insufficient data available to recommend a STEL or notations for sensitisation or skin absorption.</p> <p>Summary of data:</p> <p>Critical effect of exposure is irritation, as supported by animal and human studies. TLV-TWA derived from acute human exposure data, which suggests no irritation effects occur between 4–10 ppm.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>• 3 non-fatal exposures resulted in strong irritation, nausea and vomiting</li> <li>• Industrial chemical review classifies substance as moderately to very toxic with moderate sensitising and severe irritation potential</li> <li>• Cyclamate metabolism (e.g. from artificial sweeteners) produces cyclohexylamine, which may cause adverse effects associated with cyclamate intake</li> <li>• No adverse effects in subjects fed 5,000 mg/d of cyclamate for 7–8 d <ul style="list-style-type: none"> <li>◦ cyclohexylamine eliminated <i>via</i> urine by those able to metabolise cyclamate</li> <li>◦ cited article reports that levels of cyclohexylamine under industrial exposure conditions are unlikely to cause putative carcinogenic/teratogenic effects.</li> </ul> </li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>• IP LD<sub>50</sub>: 200 mg/kg (rats); single oral LD<sub>50</sub>: 614 mg/kg (rats)</li> <li>• Dermal LD<sub>50</sub>: 275 mg/kg (rabbits); 865–4,320 mg/kg (guinea pigs, 24 h occlusive patch)</li> <li>• 4/5 rats and 2/5 guinea pigs survived 150 ppm exposure (70 h); critical effects were irritation of eyes and respiratory tract</li> <li>• Complete destruction of the eye with 50% aqueous solution (rabbits, 1 drop)</li> <li>• Weight loss and adverse developmental effects in daily oral intake study as drinking water at 100 mg/kg (rats, guinea pigs, rabbits, 82 d)</li> <li>• Slight anaemia, decreased food intake and lower organ weights in daily feeding study with the corresponding hydrochloride salt, treatment range: 30–300 mg/kg (rats, 2 yr): <ul style="list-style-type: none"> <li>◦ NOAEL: 30 mg/kg</li> <li>◦ testicular atrophy in 100–300 mg/kg groups, no carcinogenic effects noted</li> <li>◦ similar study with 15–150 mg/kg treatment range reported reduction in litter sizes at 150 mg/kg</li> </ul> </li> <li>• Adverse reproductive and developmental effects in 6-generation mouse study at 0.5% in diet; embryotoxic effects following intraperitoneal injection to dams, fewer implants per litter with exposed males</li> <li>• Dose-dependent chromosome damage induced by intraperitoneal injection in rats, cited article concludes potential mutagenic or carcinogenic activity is uncertain.</li> </ul>		

Source	Year set	Standard
<b>DFG</b>	<b>2003</b>	<b>MAK: 2 ppm (8.2 mg/m<sup>3</sup>)</b>
<p>Summary of additional data:</p> <p>MAK derived by analogy to structurally similar dimethylamine due to insufficient chronic human or animal exposure data. Comparable RD<sub>50</sub> in mice between cyclohexylamine (50 ppm) and dimethylamine (70 ppm) support this analogy.</p> <p>Separate chronic exposure studies with rats exposed to dimethylamine respectively reported a NOAEL of 15 mg/kg/d for systemic toxicity and a LOAEL of 10 ppm for local irritation effects. Occupational intake at the MAK equates to 1.2 mg/kg/d (assuming 70 kg worker, 10 m<sup>3</sup> respired volume and 100% absorption), which is lower than both the NOAEL and LOAEL in the cited studies.</p> <p>A review of the MAK in 2017 presents an additional volunteer inhalation study with a NOAEL of 4 ppm and LOAEL of 10 ppm for eye and nose irritation (4 h).</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>Blood half-life of 3–5 h; 90% eliminated via urine</li> <li>No symptoms experienced at 4–10 ppm in workplace study (no further details provided)</li> <li>Blood pressure increase after 1 h in volunteers given to 5–10 mg/kg; concluded that 0.7–0.8 µg/mL in plasma can produce hypertensive effect</li> <li>Severe and mild irritation in 3% and 52%, respectively, of subjects in 48 h patch test with 25% solution; no effects observed in remaining subjects</li> <li>Skin notation not assigned due to relatively low systemic toxicity and uncertain if high corrosive nature contributes to reported dermal toxicity.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Reproductive study with hydrochloride salt in repeat feeding study. Treatment range: 15–150 mg/kg (rats, 2 yr): <ul style="list-style-type: none"> <li>NOAEL: 15 mg/kg for parental toxicity</li> <li>maternal toxicity at 50 mg/kg; paternal bw reduction at 100 mg/kg</li> <li>foetal weight reduced at 150 mg/kg</li> </ul> </li> <li>No LC<sub>50</sub> values available from valid methods; unreliable values are given as 1,815 ppm (rats) and 259 ppm (mice) over undocumented exposure times</li> <li>Oral LD<sub>50</sub> as undiluted or 5% aqueous solution respectively 11 or 590 mg/kg (rats)</li> <li>Systemic central nervous effects observed in dermal application study, treatment range 398–1,580 mg/kg (rabbit, n=1, no further information); death at 1,000–1,580 mg/kg,</li> <li>Target organs are liver, lungs kidneys, brain, spleen, digestive tract (rats, rabbits)</li> <li>Non-genotoxic <i>in vitro</i> or <i>in vivo</i>.</li> </ul>		
<b>SCOEL</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>OARS/AIHA</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>HCOTN</b>	<b>2001</b>	<b>TWA: 5 ppm (20 mg/m<sup>3</sup>)</b>
<p>Summary of additional data:</p> <p>Current administrative guideline of 5 ppm is considered too high following health-based risk assessment. NOAEL of 15 mg/kg for adverse reproductive effects in repeat oral intake study (rats, 2 yr) used as starting point for TWA calculation. Factors of 4 and 9 are applied to respectively account for scaling rat exposure data to humans and for intra- and interspecies differences. The resulting NOAEL for humans equates to 0.42 mg/kg/d <math>\approx</math> 1.2 ppm for an 8 h TWA (assuming 70 kg worker, 10 m<sup>3</sup> respired volume and 100% retention).</p>		

Source	Year set	Standard
Due to a lack of data the Committee could not indicate if skin notation was appropriate.		

## Secondary source reports relied upon

Source	Year	Additional information
HSE	✓ 2002	<ul style="list-style-type: none"> <li>8 h TWA: 10 ppm (41 mg/m<sup>3</sup>).</li> </ul>
NICNAS	✓ 2016	<ul style="list-style-type: none"> <li>No symptoms reported in workers exposed 4–10 ppm (&lt;8 h).</li> </ul>
IARC	✓ 1999	<ul style="list-style-type: none"> <li>Evaluated in combination with cyclamates</li> <li>Overall, not classifiable as to their carcinogenicity to humans.</li> </ul>
ECHA	✓ 2017	<ul style="list-style-type: none"> <li>Non-sensitising to skin based on animal patch test (no further information provided)</li> <li>Available reproduction/developmental data is from older studies, which are treated as unreliable due to lack of some assessment parameters. However, data indicate concern for fertility.</li> </ul>

## 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	—
HCIS	—
NICNAS	—
EU Annex	—
ECHA	—
ACGIH	Carcinogenicity – A4
DFG	—
SCOEL	NA
HCOTN	Skin
IARC	Carcinogenicity – Group 3
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<sub>50</sub> ≤1000 mg/kg: yes  
Dermal repeat-dose NOAEL ≤200 mg/kg:  
Dermal LD<sub>50</sub>/Inhalation LD<sub>50</sub> <10:  
*In vivo* dermal absorption rate >10%:  
Estimated dermal exposure at WES >10%:

**consider assigning a skin notation**

## IDLH

Is there a suitable IDLH value available? No

## Additional information

Molecular weight:	99.17
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 4.05 mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = 0.247 ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL

## Workplace exposure standard history

Year	Standard
<a href="#">Click here to enter year</a>	

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7<sup>th</sup> 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) (2003) Cyclohexylamine – MAK value documentation.

Deutsche Forschungsgemeinschaft (DFG) (2017) Cyclohexylamine – MAK value documentation.

European Chemicals Agency (ECHA) (2017) Cyclohexylamine – REACH assessment.

Health Council of the Netherlands (HCOTN) (2001) Cyclohexylamine. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/021.

International Agency for Research on Cancer (IARC) (1999) Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. IARC Monographs on the evaluation of the carcinogenic risk to humans, volume 73.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016)  
Cyclohexanamine: Human health tier II assessment – IMAP report.

UK Health and Safety Executive (HSE) (2002) EH40/2005 Workplace exposure limits.

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