2-Pyridylamine

(CAS No: 504-29-0)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands

Introduction

The present document contains the assessment of the health hazard of 2-pyridylamine by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by C de Heer, Ph.D., and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of 2-pyridylamine has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online databases Medline, Cancerlit, Toxline, and Chemical Abstracts covering the periods 1966 to 30 June 1997 (19970630/UP), 1963 to 18 June 1997 (19970618/ED), 1965 to 21 March 1997 (970321/ED), and 1967 to 1 July 1997 (970701/ED; vol 127, iss 1), respectively, and using the following key words: 2-aminopyridine, alpha-aminopyridine, 2-pyridinamine, 2-pyridylamine, and 504-29-0. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO97, NLM97). The final literature search was carried out in July 1997.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organizations: A Aalto (Ministry of Social Affairs and Health, Tampere, Finland), P Wardenbach Ph.D. (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in May 2002 did not result in information changing the committee’s conclusions.
2 Identity

name : 2-pyridylamine
synonyms : 2-aminopyridine; α-aminopyridine; 2-pyridinamine; 2-pyridylamine; α-aminopyridine; α-pyridinamine; α-pyridylamine; 1,2-dihydro-2-iminopyridine; 2-AP
molecular formula : C₅H₆N₂
structural formula :

CAS number : 504-29-0

Data from ACG91, NLM97, Ric92, Tro94.

3 Physical and chemical properties

molecular weight : 94.11
boiling point : 210.6°C
melting point : 58.1°C
flash point : 92°C (open cup); 67.78°C (closed cup)
vapour pressure : at 20°C: very low
solubility in water : highly soluble
Log P_{octanol/water} : 0.48 (experimental); 0.53 (estimated)
conversion factors (20°C, 101.3 kPa) :
1 ppm = 3.9 mg/m³
1 mg/m³ = 0.26 ppm


2-Pyridylamine is a colourless, crystalline solid with a characteristic and unpleasant odour.

4 Uses

2-Pyridylamine is an organic synthetic intermediate used in the synthesis of antihistaminic drugs and other pharmaceuticals (ACG91).

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5  **Biotransformation and kinetics**

The committee did not find information on absorption, distribution, metabolism, or excretion of 2-pyridylamine. Human case reports suggest that absorption can occur following inhalation of the dust or vapour, or possibly by dermal absorption following direct contact.

Based on physico-chemical properties, a potential for dermal absorption has been assigned (Fis90).

Because of the dermal LD$_{50}$ in guinea pigs of approximately 500 mg/kg bw, it was concluded that dermal absorption in guinea pigs occurs readily (Tro94).

6  **Effects and mechanism of action**

**Human data**

Three cases of 2-pyridylamine intoxication in humans have been reported. A fatal case of accidental exposure to 2-pyridylamine was reported in a chemical plant worker. After spillage during distillation, skin absorption, as well as inhalation of vapour probably occurred. The worker continued on his job for 1.5 hour, but 2 hours later he developed dizziness, headache, respiratory distress, and convulsions that progressed to respiratory failure and death (ACG91, Tro94).

In a non-fatal-case report, the chief symptoms described were mainly severe headache, increased blood pressure, flushing of extremities, and nausea. Air samples taken subsequently indicated a concentration of approximately 20 mg/m$^3$ (5.2 ppm). The exposure resulting in the incident was about 5 hours of duration. Recovery was complete within 24 hours (Wat50).

Finally, a more serious non-fatal case involved severe headache and weakness followed by convulsions and a stuporous state that lasted several days (exposure levels and duration not indicated) (Tro94).

**Animal data**

2-Pyridylamine was shown to cause a slight, transient eye injury when applied as a 0.02 M aqueous solution (pH>9.4) on the rabbit cornea. No other dermal or eye irritation studies were available.
The approximate LD₅₀ values for 2-pyridylamine are 200 and 50 mg/kg bw for rats and mice, respectively. In guinea pigs, where death followed convulsions, a dermal LD₅₀ of 500 mg/kg bw was reported (Tro94)*. In cats, intravenous injection of 1 mg/kg bw of 2-pyridylamine caused an increase in blood pressure and respiratory rate with symptoms of central nervous system stimulation and muscle twitching (NLM97), whereas exposure to approximately 2 mg/kg bw resulted in convulsions (Wat50).

The committee did not find data from repeated-dose toxicity studies, including carcinogenicity and reproduction toxicity, of 2-pyridylamine.

In in vitro experiments, 2-pyridylamine and other aminopyridines have been found to act on the cholinergic system, by increasing the release of acetylcholine at the neuromuscular junction. The primary site of action of aminopyridines involves the voltage-sensitive K⁺ channels of motor nerve terminals (Mol85). In another study, the effect of aminopyridine analogs on ionic conductance of the squid giant axon membrane was examined using voltage clamp and internal perfusion techniques. Reduced K⁺ currents, but no effect upon transient Na⁺ currents, were noted in a voltage-, time-, and frequency-dependent way. The effects on K⁺ channels were independent of the direction of K⁺ ion movement. The potencies of the different aminopyridine analogs tested were apparently unrelated to their pKa values (Yeh76). Blocking of the voltage-sensitive K⁺ channels leads to an enhanced calcium influx and consequently to an increase in acetylcholine release (Mol85). In addition, the voltage-sensitive K⁺ channels may be involved in the regulation of smooth muscle membrane potential. In in vitro experiments using patch-clamp techniques in smooth muscle cells isolated from rabbit cerebral (basilar) arteries, 2-pyridylamine (5 mM) inhibited voltage-dependent K⁺ currents. These voltage-dependent K⁺ channels may be involved in the regulation of arterial diameter through control of smooth muscle membrane potential in vivo (Rob94).

2-Pyridylamine (up to 2 mg/plate) was negative in mutagenicity tests in S. typhimurium strains TA98, TA100, TA1535, and TA1537 when tested with and without metabolic activation or with metabolic activation and norharman (Kam86, Ric92, Wak82).

* It is noticed that ACGIH cites other acute lethal toxicity data from former citations of Patty’s Industrial Hygiene and Toxicology, but that these are not included in the most recent (4th) edition of Patty’s. The concerning data were also not included in this document.
The committee did not find data from other genotoxicity or mutagenicity studies.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) in the Netherlands is 2 mg/m³ (0.5 ppm), 8-hour TWA.

Existing occupational exposure limits for 2-pyridylamine in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

There are no human data from which a concentration-effect relation after inhalation exposure can be estimated.

After accidental exposure of a worker to 20 mg/m³ 2-pyridylamine for 5 hours, the occurrence of a headache, increased blood pressure, flushing of extremities, and nausea was reported. Convulsions have been reported in 2 other cases of accidental intoxication with 2-pyridylamine. Results of \textit{in vitro} experiments indicate that 2-pyridylamine inhibits the voltage-sensitive K⁺ channels of the neuromuscular junction and might be related to the neurotoxic effects reported in cases of intoxication. These data suggest that the nervous system is the target organ.

In experimental animals, 2-pyridylamine was shown to cause a slight, transient eye injury when applied as a 0.02 M aqueous solution (pH>9.4) to the rabbit cornea. No other dermal or eye irritation studies were available.

Based on LD₅₀ data in rodents, the committee considers 2-pyridylamine to be ‘toxic when swallowed’ and ‘harmful in contact with skin’.

2-Pyridylamine was negative in mutagenicity tests in \textit{S. typhimurium} strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation.

The committee did not find data from other genotoxicity or mutagenicity studies or on repeated-dose toxicity, including carcinogenicity and reproduction toxicity.

The committee considers the toxicological database on 2-pyridylamine too poor to justify recommendation of a health-based occupational exposure limit.
The committee concludes that there is insufficient information to comment on the level of the present MAC-value.

**References**

ACG91  American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati OH, USA; ACGIH, 1991: 52-3.


Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; At-vejledning C.0.1.


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## Annex

Occupational exposure limits for 2-pyridylamine in various countries.

<table>
<thead>
<tr>
<th>country -organisation</th>
<th>occupational exposure limit</th>
<th>time-weighted average</th>
<th>type of exposure limit</th>
<th>note</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>the Netherlands -Ministry of Social Affairs and Employment</td>
<td>0.5 ppm 2 mg/m³</td>
<td>8 h</td>
<td>administrative</td>
<td></td>
<td>SZW02</td>
</tr>
<tr>
<td>Germany -AGS</td>
<td>0.5 ppm 2 mg/m³</td>
<td>8 h</td>
<td></td>
<td></td>
<td>TRG00</td>
</tr>
<tr>
<td></td>
<td>DFG MAK-Kommission -c-</td>
<td></td>
<td></td>
<td></td>
<td>DFG02</td>
</tr>
<tr>
<td>Great-Britain -HSE</td>
<td>0.5 ppm 2 mg/m³</td>
<td>8h</td>
<td>OES</td>
<td></td>
<td>HSE02</td>
</tr>
<tr>
<td></td>
<td>2 ppm 7.8 mg/m³</td>
<td>15 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td>Arb00b</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.5 ppm 2 mg/m³</td>
<td>8 h</td>
<td></td>
<td></td>
<td>Arb00a</td>
</tr>
<tr>
<td>USA -ACGIH</td>
<td>0.5 ppm 2 mg/m³</td>
<td>8 h</td>
<td>TLV</td>
<td></td>
<td>ACG02b</td>
</tr>
<tr>
<td>-OSHA</td>
<td>0.5 ppm 2 mg/m³</td>
<td>8 h</td>
<td>PEL</td>
<td></td>
<td>ACG02a</td>
</tr>
<tr>
<td>-NIOSH</td>
<td>0.5 ppm 2 mg/m³</td>
<td>10 h</td>
<td>REL</td>
<td></td>
<td>ACG02a</td>
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<td>European Union -SCOEL</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td>CEC00</td>
</tr>
</tbody>
</table>

- S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.
- Reference to the most recent official publication of occupational exposure limits.
- Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.