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

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1 Introduction

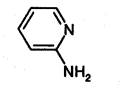
The present document contains the assessment of the health hazard of 2-pyridylamine by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by C de Heer, Ph.D., and H Stouten, M.Sc. (TNO Nutrition 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; *o*-aminopyridine; α -pyridinamine; α-pyridylamine; 1,2-dihydro-2-iminopyridine; 2-AP
molecular formula	:	$C_5H_6N_2$
structural formula	:	
CAS number	:	504-29-0

Data from ACG91, NLM97, Ric92, Tro94 .

3 Physical and chemical properties

molecular weight	:	94,11
boiling point	:	210.6ºC
melting point	:	58.1ºC
flash point	:	92ºC (open cup); 67.78ºC (closed cup)
vapour pressure	:	at 20ºC: very low
solubility in water	:	highly soluble
Log $P_{octanol/water}$	:	0.48 (experimental); 0.53 (estimated)
conversion factors (20ºC, 101.3 kPa)	:	1 ppm = 3.9 mg/m^3 1 mg/m^3 = 0.26 ppm

Data from ACG91, NLM97, Ric92, Tro94, http://esc.syrres.com.

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).

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 LD_{50} 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 LD_{50} 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).

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* 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/m^3 (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 an concentration-effect relation after inhalation exposure can be estimated.

After accidental exposure of a worker to 20 mg/m^3 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 *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 LD_{50} 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 *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

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ACG02b American Conference of Governmental Industrial Hygienists (ACGIH). 2002 TLVs® and BEIs®. Threshold Limit Values for chemical substances and fysical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2002: 14.

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

Arb00b Arbetarskyddsstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: Arbetarskyddsstyrelsen, 2000; Ordinance AFS 2000:3.

CEC00 Commission of the European Communities (CEC). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. Official Journal of the European Communities 2000; L142 (16/06/2000): 47-50.

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NIO97 US National Institute of Occupational Safety and Health (NIOSH), ed. Registry of Toxic Effects of Chemical Substances (RTECS). [CD-ROM], issue February 1997. SilverPlatter International, 1997 (last update ferric oxide file: January 1997).

NLM97 US National Library of Medicine (NLM), ed. Hazardous Substances Data Bank (HSDB). [CD-ROM], issue February 1997. SilverPlatter International, 1997 (last update 2-aminopyridine file: February 1997).

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TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

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Wak82 Wakabayashi K, Yahagi T, Nagao M, et al. Comutagenic effect of norharman with aminopyridine derivatives. Mutat Res 1982; 105: 205-10.

Wat50 Watrous RM, Schulz HN. Cyclohexamine, p-chlonitrobenzene, 2-aminopyridine: toxic effects in industrial use. Ind Med Surg 1950; 19: 317-20.

Yeh76 Yeh JZ, Oxford GS, Wu CH, et al. Interactions of aminopyridines with potassium channels of squid axon membranes. Biophys J 1976; 16: 77-81.

Annex

Occupational exposure limits for 2-pyridylamine in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
-Ministry of Social Affairs and Employment	0.5	2	8 h	administrative		SZW02
Germany						
-AGS	0.5	2	8 h			TRG00
-DFG MAK-Kommission	-[c]	-				DFG02
Great-Britain						
-HSE	0.5	2	8h	OES		HSE02
	2	7.8	15 min			
Sweden	-	-				Arb00b
Denmark	0,5	2	8 h			Arb00a
USA						
-ACGIH	0.5	-	8 h	TLV		ACG02b
-OSHA	0.5	2	8 h	PEL		ACG02a
-NIOSH	0.5	2	10 h	REL		ACG02a
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.