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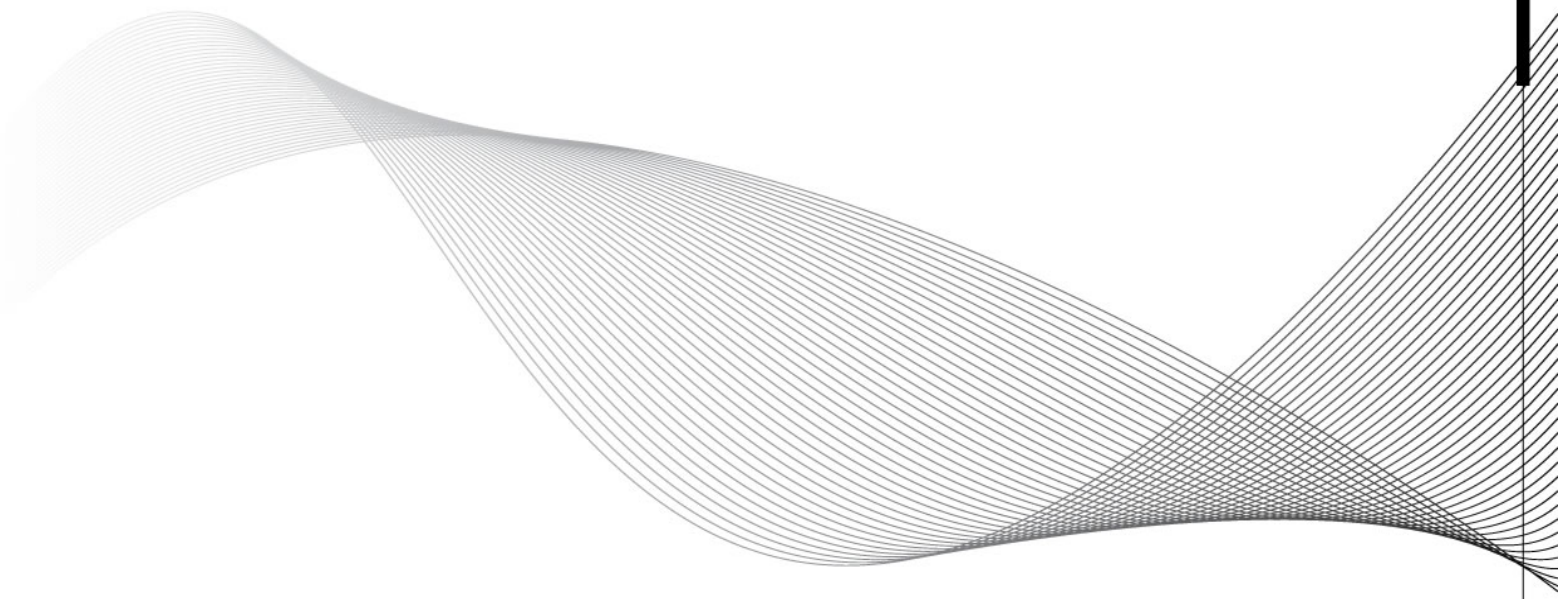

Recommendation from the Scientific Committee on Occupational Exposure Limits for pyridine

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8 hour TWA	: no recommendation made
STEL (15 mins)	: no recommendation made
Notation	: "skin"

Substance identification

Chemical name	Pyridine
CAS No:	110-86-1
Synonyms:	azabenzene, azine
Formula:	C_5H_5N
EU Classification:	

Flam. Liq. 2	H225	Highly flammable liquid and vapour
Acute Tox. 4 *	H332	Harmful if inhaled
Acute Tox. 4 *	H312	Harmful in contact with skin
Acute Tox. 4 *	H302	Harmful if swallowed

Molecular weight.	79.1
Melting point:	-41.6°C
Boiling point:	115.3°C
Vapour pressure:	2.66 kPa at 25°C
Vapour density:	2.73
Flash point:	20°C
pH value:	8.5 (0.2 M solution in water)

Conversion factor: 1 ppm=3.23 mg/m^3, 1 mg/m^3 = 0.309 ppm at 25°C

1 Occurrence/Use

Pyridine is a volatile liquid. Pure pyridine is colourless. It has an unpleasant, strong and sharp odour and a burning taste. In most individuals the odour threshold is reported to be about 0.2 ppm. Pyridine is soluble in water, alcohol, ether, oils and many other organic compounds. It is a good solvent for both inorganic and organic compounds. Pyridine is highly flammable, and may explode in contact with strong oxidisers. Contact with strong acids causes violent splattering. In fires involving pyridine, toxic gases and vapours, including oxides of nitrogen and carbon monoxide, may be released.

Pyridine is used as a solvent for paint, rubber and polycarbonate resins. A main use is in the manufacture of agricultural chemicals such as insecticides, herbicides and fungicides. It is also used in the production of piperidine and as an intermediate and solvent in the production of vitamins and drugs, dyes, textile water repellants and flavouring agents in food.

2 Health effects

2.1 Toxicokinetics

Data on toxicokinetics in humans are scarce. Most information is derived from animal experiments. Pyridine is absorbed via the digestive tract, lungs and skin and is subsequently distributed throughout the organism. The highest concentrations have been measured in blood, kidneys and urine. Pyridine is metabolised, producing mainly pyridine-N-oxide, 2-pyridone, 4-pyridone, 3-hydroxypyridine and N-methylpyridinium ions. These together with unmetabolised pyridine are excreted mainly in the urine. Pyridine is also excreted in exhaled air and faeces.The metabolic pattern varies considerably from species to species. Two healthy volunteers given 3.4 mg pyridine in orange juice (about 0.05 mg/kg body weight) excreted mostly pyridine-N-oxide (32% of the administered dose) and N-methylpyridinium (5.5% and 12% of the dose) ions in the urine collected 24 hours later. There are no reports of pyridine accumulation in the body (ACGIH 1986, ATSDR 1992).

2.2 Acute toxicity

The acute toxicity of pyridine has been studied in rats and mice. LD_{50}/LC_{50} values for rats are given as 891-1 580 mg/kg (oral), 360 mg/kg (intravenous), 866-1 150 mg/kg (subcutaneous) and about 8 000-9 000 ppm for 1 hour (inhalation). LD_{50} values for mice are 1 500 mg/kg (oral), 1 200 mg/kg (intraperitoneal, 420 mg/kg (intravenous), and 1 250 mg/kg (subcutaneous) (Rheinhardt & Britelli 1981, Jori *et al.*1983). Pyridine has a narcotic effect on experimental animals regardless of the method of administration; in high enough doses it causes weakness, ataxia, increased salivation and loss of consciousness.

The acute lethal dose of pyridine for humans has been estimated to be 0.5 to 5.0 mg/kg (OSHA 1990). OSHA states that an air concentration of 3 600 ppm constitutes an immediate danger to life (OSHA 1990). A case of acute narcosis developed by a man after he had cleaned a tank that had contained pyridine has been reported (Browning 1965). A 29-year-old man who accidentally swallowed half a cup of pyridine (approximately 125 ml) experienced nausea, dizziness, abdominal pain and lung congestion followed by death within two days (Jori *et al.* 1983).

2.3 Irritancy

Pyridine is reported to be weakly irritating to the skin of rabbits after application of 10 mg/24 hours (open Draize test) or 500 mg/24 hours (standard Draize test) (NIOSH 1989). In another study, the "irritation index" was estimated to be 1.8 on a scale of 8 (Dutertre-Catella *et al.* 1989). If pyridine was applied to damaged skin, it caused necroses on all animals. If it was applied to undamaged skin, the individual differences in sensitivity were considerable: extremely mild to severe erythema with a few cases of necrosis and no or little oedema were observed. Liquid pyridine dropped into the eyes of rabbits caused irritation of the conjunctiva, inflammation of the iris and clouding of the cornea. Pyridine was classified as strongly irritating to the eye (Duertre-Catella *et al.* 1988). An aqueous solution of 0.08 M of pyridine caused no irritation of the eye (Grant 1974).

In humans, pyridine is reported to be irritating to skin, eyes and mucous membranes (Reinhardt and Britelli 1981). Pyridine in combination with light has damaged exposed skin (Arena 1970). Pyridine has a sharp, unpleasant odour. The odour threshold for most individuals is around 0.2 ppm but perception can decrease with continued exposure (Amoore & Hautala 1983). An air concentration of 10 ppm has been reported to be almost unbearable for an unaccustomed person (OSHA 1990). The threshold for irritation of nasal mucosa, i.e. effects on the trigeminus nerve, is about 700 ppm (Amoore & Hautala 1983).

2.4 Sensitisation

The allergenic effect of pyridine is reported to be low for humans (ranked 1 on a scale of 1 to 5 in Kligman's maximisation test). There have been no reports of respiratory sensitisation to pyridine.

2.5 Effects of repeated exposure

In relation to the effects of repeated exposure, inhalation of 5 or 444 ppm of pyridine 6 hours per day for 4 days was associated with olfactory epithelial lesions in the nasal mucosa of male F344/N rats. The lesions were characterised by vacuolar degeneration of sustentacular cells, attenuation of the epithelium, loss of sensory neurons and intraepithelial luminal structures. Lesions were only slightly more severe in animals exposed to 444 ppm compared with rats exposed to 5 ppm (Nikula & Lewis 1994). In a study in rats, the animals were exposed by inhalation to levels of 10 or 50 ppm (32.3 or 161.5 mg/m^3) of pyridine vapour, five days weekly for 6 months. Increases of liver weight were found (Anonymous 1986, Gehring 1983).

Several repeated oral exposure studies have been performed. In a study in Sprague-Dawley rats (10 of each sex in each dose group), pyridine was administered by gavage at 0, 0.24, 1, 10, 25 or 50 mg/kg per day in water for 90 days. No treatment-related deaths occurred. Body weights were significantly reduced in male rats in the highest, 50 mg/kg, dose group, 70% of which also exhibited inflammatory changes in the liver compared with 10% in controls (20% in female rats). In female rats, dose-related elevation of serum cholesterol levels was registered on days 30 and 90 at 25 and 50 mg/kg. Increased liver weights occurred in female rats that received 10 mg/kg or 25 mg/kg doses. Twenty percent of these animals had inflammatory damage in livers. Liver lesions included mixed peribiliary infiltrate, bile ductule proliferation, enlarged and vacuolated hepatocytes and necrosis of hepatocytes. Effects on the central nervous system were not observed in clinical or histopathological findings. The NOAEL in this study was 1mg/kg/day (Anderson 1987).

The National Toxicology Program assessed the toxic and carcinogenic effects of pyridine in a large project including six separate studies (NTP 2000). In one study, F344/N rats (10 of each sex in each group) were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500 and 1000 ppm (equivalent to average daily doses of 0, 5, 10, 25, 55 and 90 mg/kg body weight) for 13 weeks. Liver weights of rats of both sexes exposed to doses of 250 ppm o~~r~~r more were increased. In the livers of the 500 and 1 000 ppm groups centrilobular degeneration, hypertrophy, chronic inflammation and pigmentation were increased compared with controls. In the 1 000 ppm male group, lesions consistent with α2u-globuline nephropathy were significantly increased. The NOAEL in this study was 10mg/kg/day.

In another 13-week study in male Wistar rats, the same concentrations of pyridine in water (10 in each group) were administered (equivalent average daily doses of 5, 10, 30, 60 and 100 mg/kg body weight). Incidences of centrilobular degeneration, hypertrophy, chronic inflammation and pigmentation were significantly increased in the livers of animals exposed to 500 and 1 000 ppm. The NOAEL in this study was 30 mg/kg/day.

Two separate 2-year studies were performed in rats, one in male and female F344/N rats and another in male Wistar rats. In both studies rats (50 of each sex in each concentration group) were given pyridine in drinking water at concentrations of 0, 100, 200 or 400 ppm. In the study in F344/N rats, the equivalent average daily dose was 7, 14 or 33 mg/kg body weight. In the 200 ppm groups, mean body weight decreased during the second year from 99% to 91% of the weight of control animals. In the groups exposed to 400 ppm, liver lesions were increased. These included centrilobular cytomegaly, cytoplasmic vacuolisation, periportal fibrosis, fibrosis, centrilobular degeneration and necrosis and pigmentation. Bile duct hyperplasia occurred more often in females than in controls. In the 2-year study in male Wistar rats, the average daily doses were 8, 17 or 36 mg/kg body weight. Mean body weight in groups exposed to 100 ppm or greater concentrations were significantly decreased compared with controls. In the 100 ppm group mean body weight decreased from 100% to 91% of controls during the second year. The incidence of liver lesions was signficantly increased; fibrosis and periportal fibrosis in the 200 ppm groups, centrilobular degeneration and necrosis in the 400 ppm group, and increase in pigmentation was found in all exposed groups compard with controls. Nephropathy, a common spontaneous disease in rats which increases with age, was increased in all rats (both exposed and unexposed). As a consequence of the kidney effects, mineralisation in the glandular stomach, parathyroid gland hyperplasia and fibrous osteodystrophy were observed in 100 and 200 ppm groups.

In a 13-week study in B6C3F1 mice, the same concentrations of pyridine in water (0, 50, 100, 250, 500 and 1 000 ppm) corresponding to average daily doses of 10, 20, 50, 85 and 160 mg/kg for males and 10, 20, 60, 100 and 190 mg/kg for females, were administered. Liver weights were significantly increased in male mice exposed to 100 ppm or greater and in females exposed to 250 and 500 ppm. Chemical-related lesions were not observed. Hence, in contrast to the findings above in rats, no histopathological damage was produced in the liver (or in any other organs) of the mice at up to 190 mg/kg/day.

In a 2-year study in B6C3F1 mice, groups of 50 males were exposed to pyridine in drinking water at concentrations of 0, 250, 500 or 1 000 ppm (equivalent to daily doses of 35, 65 or 110 mg/kg body weight). Groups of 50 female mice were similarly exposed at concentrations of 0, 125, 250 or 500 (equivalent to 15, 35 or 70 mg/kg body weight). Survival of exposed animals and controls was similar. Mean body weights in the 250 and 500 ppm female groups decreased from 101% to 93% and 101% to 85%, respectively, compared with control mice.

There is some information on the effects of repeated exposure in humans. An early report (Ludwig *et al.* 1935) describes two cases of pyridine *poisoning in* a factory in which workers used pyridine contaminated with mono-, di- and trimethyl derivatives of pyridine. One of the cases was a chemist who had worked with pyridine for 6 months. He suffered from a disturbed sense of balance, facial paralysis and fainting spells. The symptoms disappeared when he stopped working with pyridine. The other case was a worker who, after working with pyridine for two years, developed symptoms resembling Wernicke's pseudoencephalitis. The report gives no information about exposure levels.

Treatment of epilepsy with oral doses of 1.85 to 2.4 ml pyridine daily for 10 to 30 days resulted in symptoms such as fatigue, nausea and headache. The treatment was continued for up to two months for two patients, and resulted in severe liver and kidney damage which was fatal to one of them. As the patient was also taking other medication, including phenobarbital, the death could not specifically be attributable to pyridine (Pollock 1943).

A report (Teisinger 1947) describes seven cases of intoxication in a chemical plant where air concentrations of 6 to 13 ppm were measured. The symptoms were headaches, occasional dizziness, nervousness, sleeping difficulties, and occasional nausea and vomiting. No objective clinical findings were noted.

2.6 Mutagenicity

Pyridine has been negative in the vast majority of studies on genotoxicity. There has not been any increase in the frequency of mutations in the Ames test (Monsanto 1983, Santodonato *et al.* 1985). In one study with *Salmonella typhimuriun* TM677, however, 6 mM pyridine with microsomal activation resulted in an increased frequency of mutations (Kaden *et al.* 1974). In another study using the same strain and 25 mM of pyridine, no mutagenic effect was observed (Seixas *et al.* 1982). Various tests in *Drosophila* have been negative (Corvin & Gottlieb1978, Valencia *et al* 1985). A statistically significant. but not dose-related, increase in the frequency of sister chromatid exchanges was observed in hamster ovary cells exposed to pyridine concentrations between 1 and 5 mM (Abe & Sasaki 1977). The frequency of chromosome aberrations was not affected. Pyridine in concentrations of 0.8 to 1.3% yielded a weak increase of mitotic aneuploidy in yeast (Zimmermann FK *et al.* 1985). It was suggested that pyridine affected the tubulin in the microtubuli of the nuclear spindle. Pyridine had no effect on intercellular communication in hamster V-79 cells (Chen *et al.* 1984).

Studies conducted by the National Toxicology Program (NTP 2000) showed no mutagenicity of pyridine in four strains of *Salmonella typhimurium* (TA98, TA100, TA1535 or TA1537), with or without S9 metabolic activation enzymes. No increase in mutant frequencies was observed in L5178Y mouse lymphoma cells tested with or without S9 activation. Pyridine did not induce sister chromatid exchanges or chromosomal aberrations in cytogenic tests with cultured Chinese hamster ovary cells, with or without S9 activation. In *Drosophila melanogaster*, the results were positive for induction of sex-linked recessive lethal mutations following injection of pyridine, but did not induce reciprocal translocations in germ cells of *D. melanogaster*. No induction of chromosomal aberrations in mouse bone marrow was noted following intraperitoneal injection of pyridine.

2.7 Carcinogenicity

Fischer 344 male and female rats were administered subcutaneous doses of pyridine at 0, 3, 10, 30 or 100 mg/kg body weight twice a week for one year and sacrificed six months

after termination of the exposure (Mason *et al.* 1971). No increase of tumours was noted in the exposed animals.
In an early study (Baxter 1948), rats were given 0.20 to 0.29% pyridine in food for up to 4 months. A few of the rats developed liver nodules. The nodules were regarded as benign, since they were non-invasive and there were no metastases.

The three 2-year studies on rats and mice described under "Animal Data" provide new evidence of carcinogenicity of pyridine in rats and mice (NTP 2000). The study on male and female F344/N rats showed an increased incidence of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in male rats exposed to 400 ppm of pyridine in drinking water (equivalent to an average daily dose of 33 mg/kg body weight) compared with controls and exceeded historical control ranges. There was also an increase of renal tubule hyperplasia in that group of animals. Mononuclear cell leukemia was increased in female rats receiving 200 and 400 ppm (daily dose 14 and 33 mg/kg, respectively). The incidence in control rats was 26.5%, in the 200 ppm group 45.4%, and in the 400 ppm group 48.7% (adjusted rates). The conclusion based on renal tubule neoplasms in male F344/N rats was "*some evidence of carcinogenic activity*" according to the characterisation of carcinogenic activity by five categories used by the National Toxicology Program. The categories refer to strength of the experimental evidence and not to the potency or mechanism. The increase in mononuclear cell leukemia in female ratswas concluded to be "*equivocal evidence of carcinogenic actvivty*".

In the 2-year study on male Wistar rats, testicular interstitial cell adenoma was significantly increased in rats exposed to 400 ppm of pyridine (equivalent daily dose 36 mg/kg body weight); the ajusted incidence rate was 36.6%, compared with 12.3% in control rats. A slight, non-significant, increase in interstitial cell hyperplasia was noted in rats exposed to 17 or 36 mg/kg. Based on the increased incidence of testicular cell adenoma, the conclusion was "*equivocal evidence of carcinogenic activity*".

In the NTP 2-year study in B6C3F1 mice the incidence of hepatocellular neoplasms, including hepatoblastomas, in exposed male and female mice was clearly related to pyridine exposure. The adjused rate of hepatocellular carcinoma was 78.7% in the male 250 ppm group (32.3% in controls) and 55.0%, 78.1% and 97.1% in the female 125, 250, and 500 ppm groups (29.8% in controls). Corresponding adjusted rates for hepatoblastomas in male 250 ppm and 500 ppm groups were 41.2% and 49.8%, respectively (4.5% in controls), and in female 250 ppm and 500 ppm groups 21.6% and 39.6%, respectively (2.4% in controls). Many of the animals had multiple hepatocellular neoplasms. The incidences in exposed animals, both male and female, exceeded the historical control ranges for drinking water studies. The result of a 2-year experiment on mice was concluded *as "clear evidence of carcinogenic activity"* of pyridine.

2.8 Reproductive toxicity

There is a NTP study on rats suggesting adverse effects on the reproductive system. 10 female Fisher 344 rats were exposed to 0, 250, 500 and 1 000 ppm pyridine in drinking water for 13 weeks. Average daily doses were 0, 25, 55 and 90 mg/kg bw. At the highest dose level, a lower body weight was accompanied by reduced weight of epididymis and testes in males. In females, average oestrus cycle length was significantly increased at the highest dose level (National Toxicology Program, 1997). Studies on developmental toxicity or on fertility are not available.

A similar study on mice did not reveal any reproductive effects. Groups of 10 male and female B6C3F$_1$ mice were exposed to 0, 250, 500 or 1 000 ppm pyridine in drinking water for 13 weeks. Average daily doses were 0, 55, 85 and 160 mg/kg bw for males and 0, 60,

100 and 190 mg/kg bw for females. Spermatozoal motility was slightly, but significantly, decreased at all three dose levels tested. There were no significant differences in oestrus cycle lengths in females (National Toxicology Program, 1997).

3 Recommendation

The critical effect after short-term exposure is irritation of the mucous membranes of the upper respiratory tract and eyes, together with acute effects on the central nervous system. The critical identified long-term effects in experimental animals are on the liver and kidney; however, little work has been done on the potential long-term effects of inhaled pyridine, particularly on the respiratory tract.
The NTP 2-year studies in rats and mice have indicated that pyridine has a carcinogenic effect in mice and rats (NTP 2000). However, it appears that pyridine is not genotoxic. The mechanisms by which the rodent tumours were produced have not been fully elucidated, but it is likely that they were non-genotoxic in nature. Their relevance to human health is doubtful; even if relevant, they would not occur if exposures were maintained below the levels at which precursor toxic effects occur.

From the data available, SCOEL concluded that it is not possible to derive a health-based limit value for pyridine. An exposure level of 5 ppm produced lesions in the nasal olfactory epithelium of rats after only 4 days (6 hours per day), with no NOAEL having been identified. The most likely explanation for this finding is that it is the result of metabolic activation of pyridine at this site. There is uncertainty about what the consequences would be in the rat nasal epithelium of repeated exposure for a much longer period. There is also uncertainty about the extrapolation of any such findings in the rat to predictions of consequences for human health. Nevertheless, the rat nasal lesions are of major concern, so that SCOEL felt that is not possible to identify with confidence a level of inhalation exposure that does not pose a concern of toxicity to the upper respiratory tract in humans.

These considerations, and early reports of adverse health effects in humans exposed to airborne concentrations reportedly in the range 6-13 ppm, led SCOEL to recommend that occupational exposures to pyridine should be maintained well below 5 ppm.

As pyridine can be absorbed through the skin and consequently, could pose a threat of systemic toxicity, a "Sk" notation is justified.

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