PYRIDINE

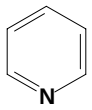
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 110-86-1
Deleted CAS Reg. Nos: 6999-00-4; 45410-39-7; 62301-32-0; 82005-06-9; 85404-19-9; 85404-20-2; 152758-95-7; 163392-20-9
Chem. Abstr. Name: Pyridine
IUPAC Systematic Name: Pyridine
Synonyms: Azabenzene; azine

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_5H_5N Relative molecular mass: 79.10

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with a disagreeable odour (Budavari, 1998)
(*b*) *Boiling-point*: 115.2 °C (Lide & Milne, 1996)
(*c*) *Melting-point*: –41.6 °C (Lide & Milne, 1996)
(*d*) *Density*: 0.9819 g/cm^3 at 20 °C (Lide & Milne, 1996)
(*e*) *Spectroscopy data*: Infrared (prism [15]; grating [12]), ultraviolet [9], nuclear magnetic resonance (proton [10200, V96]; C-13 [1201]) and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996)
(*f*) *Solubility*: Miscible with water, acetone, benzene, chloroform, diethyl ether and ethanol (Lide & Milne, 1996)

(*g*) *Volatility*: Vapour pressure, 2.76 kPa at 25 °C (Lide & Milne, 1996); relative vapour density (air = 1), 2.73 (Verschueren, 1996)
(*h*) *Stability*: Highly flammable; flash point, 20 °C (closed cup) (Budavari, 1998); explosive limits, 12.4% (upper), 1.8% (lower) by volume in air (American Conference of Governmental Industrial Hygienists, 1999)
(*i*) *Octanol/water partition coefficient (P)*: log P, 0.60/0.65 (Hansch *et al*., 1995)
(*j*) *Conversion factor*[1]: $mg/m^3 = 3.24 \times ppm$

1.1.4 *Technical products and impurities*

Pyridine is commercially available in several grades for specific applications. Specifications vary according to country but are usually greater than 99.8% purity by gas chromatographic analysis (Scriven *et al*., 1996; Burdick & Jackson, 1997).

Trade names for pyridine include: CP 32.

1.1.5 *Analysis*

Selected methods for the analysis of pyridine in various matrices are given in Table 1.

1.2 Production

Pyridine was first synthesized in 1876 from acetylene and hydrogen cyanide (Shimizu *et al.*, 1993). A more plentiful source was found in coal tar, the condensate from coking ovens in the steel industry. Pyridine bases are found in the light-oil and middle-oil fractions from coal tar and comprise pyridine, the picolines and higher homologues. Pyridine has been produced commercially from coal-tar sources since the 1920s. During the 1950s, synthetic processes were developed to provide alternatives to isolation from coal-tar sources (Santodonato *et al.*, 1985; Scriven *et al.*, 1996). There are few selective commercial processes for preparing pyridine and its derivatives, and almost all manufacturing processes produce pyridine along with a series of alkylated pyridines in admixture. The reaction of aldehydes or ketones with ammonia is the most general synthetic reaction for the manufacture of pyridine bases and allows the preparation of various pyridine derivatives. Reaction of acetaldehyde and formaldehyde with ammonia is the most widely used method for pyridine production (Scriven *et al*., 1996).

Pyridine can also be prepared from cyclopentadiene by ammoxidation, or from 2-pentenenitrile by cyclization and dehydrogenation. Furfuryl alcohol or furfural reacts with ammonia in the gas phase to give pyridine (Scriven *et al*., 1996).

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[1] Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming a temperature of 25 °C and a pressure of 101 kPa

Table 1. Selected methods for the analysis of pyridine

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Air	Adsorb (charcoal); desorb (dichloromethane)	GC/FID	0.02 mg/sample	Eller (1994) [Method 1613]
Water, soil, municipal waste	Add isotope-labelled analogue; extract with dichloromethane; dry over sodium sulfate; concentrate	GC/MS	5 µg/L	Environmental Protection Agency (1995) [Method 1665]
Solid waste matrices[b]	Solvent extraction or direct injection (with azeotropic distillation) into capillary GC column	GC/FID	9–21 µg/L (aqueous matrices); 0.08–0.20 mg/kg (solid matrices)	Environmental Protection Agency (1996a) [Method 8015B]
	Direct injection (with azeotropic distillation) into capillary GC column	GC/MS	4 µg/L	Environmental Protection Agency (1996b) [Method 8260B]

[a] Abbreviations: GC, gas chromatography; FID, flame ionization detection; MS, mass spectrometry
[b] Includes: groundwater, sludges, caustic and acid liquors, waste solvents, oily wastes, mousses, tars, fibrous wastes, polymeric emulsions, filter cakes, spent carbons, spent catalysts, soils and sediments

Information available in 1999 indicated that pyridine was manufactured by four companies in the United States, three companies in China, two companies each in Germany, India, Japan and United Kingdom, and one company each in Argentina, Belgium, France, Hungary, Israel, Italy, the Russian Federation, Spain, Taiwan and Ukraine (Chemical Information Services, 1999).

1.3 Use

Pyridine is widely used as a solvent in organic chemistry and in industrial practice. Pyridine is an effective, basic solvent that is relatively unreactive, which makes it a good acid scavenger. Pyridine is the solvent of choice for acylation and dehydrochlorination reactions. It is also used as a solvent for paint, rubber, pharmaceuticals, polycarbonate resins and textile water repellants. Large amounts of pyridine are used as an intermediate in the manufacture of substituted pyridines, piperidine, agrochemicals (herbicides: diquat, paraquat; insecticide: chlorpyrifos; fungicide: pyrithione), pharmaceuticals and other products (Santodonato *et al.*, 1985; Agency for Toxic Substances and Disease Registry, 1992; Shimizu *et al.*, 1993; Scriven *et al.*, 1996).

1.4 Occurrence

1.4.1 *Natural occurrence*

Pyridine is found among the volatile components of black tea (Vitzthum *et al.*, 1975) and in the leaves and roots of *Atropa belladonna* (Burdock, 1995).

1.4.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1999), as many as 43 000 workers in the United States were potentially exposed to pyridine. Occupational exposure may occur by inhalation and dermal contact during its production by synthesis or by treatment and distillation of crude coal-tar, during the processing of oil-shale and at coke-oven works. Exposure may also occur during its wide use as a chemical intermediate and/or solvent (Santodonato *et al.*, 1985; Agency for Toxic Substances and Disease Registry, 1992). Laboratory use appears to account for a large number of workers potentially exposed (Santodonato *et al.*, 1985; NOES, 1999).

Few data, especially recent data, are available on occupational exposure levels of pyridine. In 1978, the United States Pyridine Task Force of the Interagency Testing Committee reported that in United States workplaces where pyridine was manufactured or used as a chemical intermediate or as a solvent, workers were exposed to 8-h time-weighted average (TWA) pyridine concentrations ranging from 0.008 to 1.0 ppm [0.026 to 3.24 mg/m^3]. Technicians working in quality control and research and development laboratories of one of the pyridine manufacturers were exposed to TWA concentrations (measured over 6-h periods) of no more than 0.09 ppm [0.29 mg/m^3] (Santodonato *et al.*, 1985).

A few studies have evaluated exposure levels in industries where pyridine originates from coal or coal-tar or where coal-tar products are processed or used. In a pyridine production shop of a coal-tar manufacture in the former USSR, pyridine levels were 7.5–10 mg/m^3 and occasionally reached 20 mg/m^3 (Izmerov, 1984). Mašek (1981) measured airborne concentrations in various industries in former Czechoslovakia. Values ranged from 0.005 to 2.98 mg/m^3 [0.0015–0.92 ppm] in coking plants, from 0.005 to 0.135 mg/m^3 [0.0015–0.042 ppm] in blast furnaces and steel works and from 0.010 to 0.630 mg/m^3 [0.0031–0.195 ppm] in rolling mills and foundries. More recently, Bienik *et al.* (1993) reported personal exposure levels ranging from 0.002 to 0.7 mg/m^3 [0.00062–0.22 ppm] (24 workers) in a Polish carbochemical plant. A study in a United States laboratory conducting research on coal conversion technology found no level of pyridine greater than 0.2 ppm [0.65 mg/m^3] throughout the 1979–82 sampling period (Dreibelbis *et al.*, 1982).

Air samples were collected in the moulding and pouring departments of a United States iron foundry using a phenolic urethane binder. The two-day average level of pyridine, emitted as a breakdown product of 4-phenylpropylpyridine used as a binder

catalyst, was 5.9 ppm [19.1 mg/m^3] in the moulding area (Apol, 1982). Pyridine as a possible pyrolysis product was not detected (< 0.1 ppm) [0.32 mg/m^3] near a nylon injection-moulding operation of a United States electrical components production plant (Hartle & Erhenberg, 1985).

1.4.3 *Environmental occurrence*

The production of pyridine and its wide use as a solvent and as an intermediate in the synthesis of piperidine and a wide variety of drugs, insecticides and herbicides and chemicals used in rubber vulcanization may result in its release into the environment (Jori *et al.*, 1983; Agency for Toxic Substances Disease Registry, 1992; Environmental Protection Agency, 1999). Pyridine occurs in the environment as a by-product of coal gasification (Stuermer *et al.*, 1982).

Pyridine and its homologues are produced in coking procedures and present in the non-condensable gases. Pyridine is also present in coal-tar and as a component in creosote (Agency for Toxic Substances Disease Registry, 1992; Dutch Ministry of Social Affairs and Employment, 1993).

(*a*) *Air*

Pyridine has rarely been detected in ambient rural or urban air except in the vicinity of industrial or waste-treatment facilities (Hawthorne & Sievers, 1984; Shah & Heyerdahl, 1988; US Agency for Toxic Substances Disease Registry, 1992). Atmospheric emission of pyridine has been detected at a concentration of 13 μg/m^3 in the air in the vicinity of an oil-shale wastewater facility (Hawthorne & Sievers, 1984). Pyridine is released into the atmosphere as fugitive emissions from coal gasification and oil-shale processing facilities and from iron working and coking plants (Junk & Ford, 1980; National Toxicology Program, 1997).

According to the Environmental Protection Agency Toxics Release Inventory (TRI), air emissions of pyridine from 43 industrial facilities in 1997 were approximately 46 325 kg in the United States (Environmental Protection Agency, 1999).

(*b*) *Water*

Pyridine in water may partition to soils and sediments to an extent that depends on the pH of the water, and to a lesser extent, the organic carbon content of the soil (Agency for Toxic Substances Disease Registry, 1992).

Surface water discharges of pyridine from 43 industrial facilities in 1997 in the United States amounted to 247 kg; in addition, underground injection of pyridine amounted to 278 290 kg as reported in the Toxics Release Inventory (US Environmental Protection Agency, 1996c).

Pyridine has been found in both subsurface and groundwater as a result of industrial activities such as synthetic fuel production and chemical manufacturing (Sims & O'Loughlin, 1989). Pyridine is a component in the basic fraction of oil-shale

retort waters (Leenheer & Stuber, 1981) with typical concentrations of 20–100 mg/L (Zhu *et al.*, 1988). Pyridine was detected at a concentration of about 5 mg/L in Australian oil-shale retort water (Dobson *et al*., 1985). It was detected in one of two oil-shale processing effluents at a concentration of 152 μg/L, but not in coal gasification plant effluents (Pellizzari *et al.*, 1979; cited in Agency for Toxic Substances Disease Registry, 1992). Pyridine was found at levels of 0.82, 49 and 53 ppb (μg/L) in groundwater samples from three wells near an underground coal gasification site in northeastern Wyoming (Stuermer *et al*., 1982).

(*c*) *Soil and sediments*

Pyridine (and its derivatives) are water-soluble and do not readily bind to organic constituents of soil and aquifer materials. They may, therefore, be transported through aquifer materials, sediments and soils and thus contaminate rivers and estuaries (Liu & Kuo, 1997).

Although pyridine releases to land from industrial sources in the United States totalled an estimated 510 kg in 1988 as reported in the Toxics Release Inventory (Environmental Protection Agency, 1996c), release of only 2 kg to land was reported in 1997 (Environmental Protection Agency, 1999).

(*d*) *Food*

Pyridine has been isolated in the volatile components from cooked beef (‘sukiyaki’) in Japan (Shibamoto *et al*., 1981), fried chicken in the United States (Tang *et al*., 1983), fried bacon (Ho *et al*., 1983), Beaufort cheese (Dumont & Adda, 1978), black tea aroma (Vitzthum *et al*., 1975) and coffee aroma (Aeschbacher *et al*., 1989).

(*e*) *Tobacco smoke*

Pyridine has been detected as a component of tobacco and marijuana smoke (Schmeltz & Hoffmann, 1977; Curvall *et al.*, 1984; Eatough *et al.*, 1989). It has been found in tobacco smoke at 21–32 μg per cigarette (IARC, 1986). In indoor air, pyridine has been detected at concentrations as high as 16 μg/m^3 in indoor air contaminated with cigarette smoke (Brunnemann *et al.*, 1991; cited in Agency for Toxic Substance Disease Registry, 1992). Otson *et al.* (1994) reported a pyridine level of 6 μg/m^3 in air in Canadian homes.

1.5 Regulations and guidelines

Occupational exposure limits and guidelines for pyridine are presented in Table 2.

The Food and Drug Administration (1999) permits the use of pyridine as a synthetic flavouring substance or adjuvant generally recognized as safe in foods in the United States.

Table 2. Occupational exposure limits and guidelines for pyridine[a]

Country	Year	Concentration (mg/ m^3)	Interpretation[b]
Australia	1993	15	TWA
Belgium	1993	15	TWA
Czech Republic	1993	5	TWA
		10	STEL
Denmark	1993	15	TWA
Egypt	1993	15	TWA
Finland	1998	15 (sk)	TWA
		30	STEL
France	1993	15	TWA
		30	STEL
Germany	1999	15	TWA
Hungary	1993	5 (sk)	TWA
		10	STEL
Ireland	1997	15	TWA
		30	STEL
Netherlands	1997	0.9	TWA
Philippines	1993	5	TWA
Poland	1998	5 (sk)	TWA
Russian Federation	1993	5	STEL
Sweden	1993	15	TWA
		30	STEL
Switzerland	1993	15	TWA
		30	STEL
Turkey	1993	15	TWA
United Kingdom	1997	15	TWA
		30	STEL
United States			
ACGIH	1999	15	TWA
NIOSH	1999	15	TWA
OSHA	1999	15	TWA

[a] From Finnish Ministry of Social Affairs and Health (1998); American Conference of Governmental Industrial Hygienists (ACGIH) (1999); Deutsche Forschungsgemeinschaft (1999); Occupational Safety and Health Administration (OSHA) (1999)

[b] TWA, time-weighted average; STEL, short-term exposure limit; sk, skin notation

[c] These countries follow the recommendations of the ACGIH threshold limit values: Bulgaria, Colombia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

2. Studies of Cancer in Humans

Cohort study

A cohort of 729 male workers was set up at three plants manufacturing 4,4′-bipyridyl from pyridine in the north-west of England, including all employees working in 1983 at the time when the cohort was established and all past employees in the manufacturing process since 1961 (Paddle *et al.*, 1991). The mortality was assessed up to the end of 1985; 3.4% of the cohort could not be traced. Reference rates from England and Wales were obtained and corrected upwards to account for higher mortality rates in the area. Overall, 75 deaths were observed versus 96.3 expected (standard mortality ratio [SMR], 0.8 [95% confidence interval (CI), 0.6–1.0]), including 29 cancer deaths versus 27.1 expected (SMR, 1.1 [95% CI, 0.7–1.5]). When a 10-year latency was imposed between the start of exposure and the start of follow-up, an excess of mortality from lung cancer was observed (SMR, 1.7 [95% CI, 0.9–3.1]), increasing to 2.1 after 15 years. Additional analysis by job, plant and categories of exposure to chemicals in a nested case–referent study did not identify any risk factor for lung cancer except for exposure to diethylene glycol dimethyl ether (diglyme). An examination of the exposure levels and time since exposure of the lung cancer cases did not support a causal interpretation. Data on the relationship between lung cancer and exposure to pyridine were not reported. [The Working Group noted that the precise list of chemicals investigated was not mentioned.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F_1 mice, seven weeks of age, were exposed to pyridine (purity, 99.8%) in the drinking-water at concentrations of 0, 250, 500 or 1000 mg/L (ppm), equivalent to an average daily dose of 0, 35, 65 or 110 mg/kg bw, for males and 0, 125, 250 or 500 ppm [mg/L], equivalent to an average daily dose of 15, 25 or 70 mg/kg bw, for females for 104 weeks (males) or 105 weeks (females). Mean body weights of males were similar to those of the controls; mean body weights of 250- and 500-ppm females were lower than those of controls from weeks 89 and 73, respectively. Survival of exposed males and females was similar to that of the controls. Statistical analyses were carried out using the Poly-3 test. Hepatocellular adenomas occurred at an increased incidence in males: 29/50, 40/50 ($p = 0.003$), 34/49 and 39/50 ($p = 0.011$) in control, low-, mid- and high-dose mice, respectively. The incidence of hepatocellular carcinomas in males was: 15/50 control, 35/50 low-dose,

41/49 mid-dose and 40/50 high-dose mice, respectively ($p < 0.001$, pairwise comparisons for all treated groups). The incidence of hepatoblastomas in males was: 2/50, 18/50, 22/49 and 15/50 ($p < 0.001$, pairwise comparisons for all treated groups) in control, low-dose, mid-dose and high-dose mice, respectively. In female mice, the incidence of hepatocellular carcinomas was increased in a dose-related manner: 13/49 control, 23/50 low-dose, 33/50 ($p = 0.014$) mid-dose and 41/50 high-dose mice ($p < 0.001$). The incidence of hepatoblastomas was also significantly increased: 1/49 control, 2/50 low-dose, 9/50 ($p = 0.007$) mid-dose and 16/50 high-dose mice ($p < 0.001$) (National Toxicology Program, 1997).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, eight weeks of age, were given drinking-water containing 0, 100, 200 or 400 ppm pyridine (purity, 99.8%) for 103 weeks (males) or 104 weeks (females). Average daily doses were 0, 7, 14 and 33 mg/kg bw. Mean body weights of 200- and 400-ppm males after weeks 73 and 6, respectively, and females after weeks 61 and 9, respectively, were less than those of controls [statistical significance not reported]. Survival of exposed males and females was not significantly different from that of controls. As shown in Table 3, the incidence of renal tubule adenomas in male rats was increased, whether single sections or single and multiple sections combined were evaluated (National Toxicology Program, 1997).

Table 3. Incidence of renal tubule tumours in male Fischer 344 rats fed pyridine in the diet

Dose	Number of animals			
	0	100 ppm	200 ppm	400 ppm
Single sections				
Renal tubule adenomas	1/50	0/48	2/50	6/49*
Renal tubule carcinomas	0/50	1/48	0/50	0/50
Step sections				
Renal tubule adenomas	1/50	3/48	5/50	9/49**
Single section and step sections combined				
Renal tubule adenomas	2/50	3/48	6/50	10/49**
Renal tubule carcinomas	0/50	1/48	0/50	0/49
Renal tubule adenomas and carcinomas	2/50	4/48	6/50	10/49**

From National Toxicology Program (1997)
* $p < 0.05$, Poly-3 test
** $p < 0.01$, Poly-3 test

In a concurrent experiment, groups of 50 male Wistar rats, seven weeks of age, were given drinking-water containing 0, 100, 200 or 400 ppm pyridine (purity, 99.8–0.6%), resulting in average daily doses of approximately 8, 17 or 36 mg/kg bw, for 104 weeks. Mean body weights of rats exposed to 100, 200 or 400 ppm were significantly lower than those of controls, beginning at weeks 69, 49 and 6, respectively. Survival of rats exposed to 200 or 400 ppm pyridine was significantly lower than that of the controls. The incidence of testicular adenoma in rats exposed to 400 ppm was significantly increased compared with controls: 5/50 controls, 6/49 low-dose, 4/49 mid-dose and 12/50 high-dose ($p = 0.012$, pairwise comparison). In contrast to the Fischer rats, renal tubule cell tumours were not observed at increased incidence, even after step sectioning (US National Toxicology Program, 1997). [The Working Group noted that the National Toxicology Program cited a historical control range for testicular adenomas in Wistar rats (0–22%) (Walsh & Poteracki, 1994), the upper limit of which was similar to the incidence in high-dose males seen in this study.]

3.2 Subcutaneous administration

Rat: Groups of 10, 20, 30 or 40 male and 10, 20, 30 or 40 female Fischer 344/N rats, four weeks of age, were injected subcutaneously with 0, 3, 10, 30 or 100 mg/kg bw pyridine (commercial product) in physiological saline twice a week for 52 weeks. The animals were observed for a further six months. Body weights were similar in treated and untreated animals. Distributed across all groups, only three animals died by 12 months and eight by 18 months. There was no increase in the incidence of tumours either at the injection site or at any other site (Mason *et al*., 1971).

3.3 Genetically modified mouse models

Groups of 15–20 hemizygous female Tg.AC mice (zeta-globin promoted v-Ha-*ras* on an FVB background), 14 weeks of age, were administered pyridine [purity not specified] in 200 μL acetone topically on shaved skin in the interscapular region five times per week at doses of 0, 1.5, 3.0 or 6.0 mg per mouse for 20 weeks. Concurrent negative control groups of 15 mice were treated with 200 μL acetone alone. A group of 15 animals was treated topically with 12-*O*-tetradecanoylphorbol 13-acetate (TPA) (approximately 99% pure) dissolved in 200 μL acetone at a dose of 1.25 μg per mouse three times per week. Skin papillomas were observed at the end of the study in 1/15, 2/15, 0/14 and 1/20 in the untreated control, low-dose, mid-dose and high-dose animals, respectively. Skin papillomas were observed in 15/15 TPA-treated mice (Spalding *et al*., 2000).

Heterozygous male and female $p53^{+/-}$ mice (C57BL/6-Trp53(+/–)tm1Dol;N5), eight to 11 weeks of age, were given pyridine [purity not specified] in the drinking-water *ad libitum* for seven days per week for 26 weeks at doses of 0, 250, 500 or 1000 mg/L (ppm) for males and at 0, 125, 250 or 500 ppm for females. There was no increase in the incidence of tumours in any of the treated groups (Spalding *et al*., 2000).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The fate of pyridine was examined in two healthy male subjects, who each received an oral dose of 3.4 mg [^{14}C]pyridine [approx. 0.01 mg/kg bw] in orange juice. A total of 65 and 68% of the ^{14}C-dose was recovered in the 0–24-h urine of the two subjects, respectively, and two metabolites were identified: pyridine *N*-oxide, which accounted for 32% of the dose, and *N*-methylpyridinium ion, accounting for 6 and 12% of the dose, respectively. Some 25% of the dose was not characterized (D'Souza *et al.*, 1980; Damani *et al.*, 1982).

4.1.2 *Experimental systems*

Pyridine is metabolized in animals by oxidation at the nitrogen atom, giving pyridine *N*-oxide, and at all carbon atoms of the ring, giving 2- and 4-pyridone and 3-hydroxypyridine. In addition, it undergoes *N*-methylation, yielding the quaternary ammonium ion *N*-methylpyridinium. The relative contributions of these pathways to the overall fate of pyridine were examined by Damani *et al.* (1982) who administered [^{14}C]pyridine intraperitoneally to rats, mice, guinea-pigs, hamsters, gerbils, rabbits and cats at a dose of 7 mg/kg bw. At least 50% of the administered ^{14}C was recovered in the urine of the animals and the amounts of the various specific metabolites differed markedly between species, as shown in Table 4. Only small amounts (0.4–5% of dose) of unchanged pyridine were found in most species, but cats excreted 14% and rabbits 25% of the dose in this form. The extent of *N*-oxidation varied widely between species, from 0.3% of dose in rats to 39% in hamsters. Pyridine *N*-oxide was not detected in rabbit urine. The excretion of *N*-methylpyridinium also varied between species, being lowest in gerbils (~2% of dose) and highest in cats (51% of dose). The major *C*-oxidation product was 4-pyridone, which ranged from 4% of the dose in hamsters to 19% in rabbits. 2-Pyridone and 3-hydroxypyridine were minor metabolites in all species, the former being absent from the metabolic profile in rabbits. Mice did not oxidize pyridine at any carbon atom of the ring. The occurrence of additional metabolic pathways is suggested by the excretion of unidentified products, accounting for up to 37% of the dose, in all species except guinea-pigs and cats (Damani *et al.*, 1982). These pathways include glucuronidation of 3-hydroxypyridine, previously observed in rabbits (Smith, 1953).

There is a dose-dependence in the metabolism of pyridine. At low doses of pyridine, *N*-methylation may be the preferred route of biotransformation, while at higher doses, such as 40 mg/kg bw, the extent of *N*-oxidation varied from some 10% in rats to 20–40%

Table 4. Species variations in the metabolic *C*- and *N*-oxidation and *N*-methylation of [^{14}C]pyridine in various laboratory animals *in vivo*

	Total ^{14}C recovery	% of dose in 0–24-h urine						
		Pyridine	*N*-Methyl-pyridinium[a]	2-Pyridone	3-Hydroxy-pyridine	4-Pyridone	Pyridine *N*-oxide[b]	Unknown(s)
Rat	48	2	4 (5)	1	2	10	0.5 (0.3)	28
Mouse	66	2	21 (12)	ND	ND	ND	5 (6)	37
Guinea-pig	66	5	31 (30)	2	2	18	9 (8)	0
Hamster	67	0	17 (26)	1	0.3	4	39 (37)	6
Gerbil	52	0.4	1 (2 and 3)	1	1	7	8 (10)	34
Rabbit[c]	77	25	13 (15)	0	4	19	0	17
Cat[d]	75	14	51 (40)	2	1	10	3	0
Human	66	ND	(6 and 12)	ND	ND	ND	(32)	~25

From Damani *et al.* (1982). Values obtained by high-performance liquid chromatography
ND, not determined
[a] Values in parentheses obtained by reverse isotope dilution
[b] Values in parentheses obtained by gas chromatography
[c] 0–72-h urine
[d] 0–48-h urine

in mice, hamsters, guinea-pigs, rabbits and ferrets (Damani *et al.*, 1982). In rats, the formation of *N*-methylpyridinium ion as a percentage of administered dose fell from 10 to 0.8% with increasing dose over the range 1–500 mg/kg bw (D'Souza *et al.*, 1980). The occurrence of *N*-methylation was similar whether pyridine was given orally or by intraperitoneal injection. In contrast, guinea-pigs excreted 31% of a dose as *N*-methylpyridinium independently of dose (either 1 or 7 mg/kg bw, as for rats): this was unaffected by the route of administration but the excretion decreased to 2% when the intraperitoneal dose was 500 mg/kg bw. The low *N*-methylation capacity of the rat was not enhanced by pre-treatment and dietary supplementation with DL-methionine, the precursor of the methyl donor *S*-adenosylmethionine.

D'Souza *et al*. (1980) examined the further metabolism of *N*-methylpyridinium. Rats and guinea-pigs given *N*-methyl[^{14}C]pyridinium by intraperitoneal injection excreted 53% and 85% respectively of the dose in the 0–24-h urine. In both species, > 95% of urinary ^{14}C was present as unchanged *N*-methylpyridinium.

4.2 Toxic effects

4.2.1 *Humans*

Ingestion of approximately 500 mg/kg bw pyridine by a 29-year-old man caused nausea, dizziness, abdominal pain and lung congestion followed by death after 43 h. Inhalation by workers of pyridine vapours at a concentration of about 125 ppm [405 mg/m^3] pyridine for 4 h per day for one to two weeks resulted in headache, dizziness, insomnia, nausea and anorexia (Jori *et al.*, 1983).

4.2.2 *Experimental systems*

Pyridine citrate given in the diet (0.7–1.0%) to young adult male rats [strain not stated] resulted in the death of most of the animals within two or three weeks (Baxter, 1947). Clinical and histopathological examination revealed acute hepatic and renal injury, followed by regenerative changes, cirrhosis and chronic renal injury. Increasing the choline content of the diet at the same time that the pyridine level was also being increased caused a marked reduction in fatty degeneration and fibrosis of the liver without any significant reduction in the severity and extent of the acute necrosis.

In rats, the LD_{50} of pyridine after a single subcutaneous injection was estimated to be 866 mg/kg bw (Mason *et al.*, 1971). It is of interest to note that the intraperitoneal LD_{50} of *N*-methylpyridinium, a major metabolite in some species, is 0.22 g/kg bw in mice, compared with 1.2 g/kg bw for pyridine (D'Souza *et al.*, 1980). A dose of 100 mg/kg bw administered subcutaneously twice weekly for one year to male and female Fischer 344 rats led to significant retardation of weight gain (Mason *et al.*, 1971). Inhalation of 5 ppm [16 mg/m^3] pyridine for 6 h per day for four days caused olfactory epithelial lesions in male Fischer 344/N rats. These included vascular degeneration of sustentacular cells, focal, marked attenuation of the epithelium, loss of neurons and

the presence of intraepithelial luminal structures (Nikula & Lewis, 1994). In male Sprague-Dawley rats, a single intraperitoneal dose of pyridine (200 mg/mL saline; 1 mmol/kg bw) caused a significant increase in serum level of sorbitol dehydrogenase, indicating liver damage (Felten *et al.*, 1998).

In male New Zealand White rabbits, pyridine treatment (one intraperitoneal injection of 100 mg/kg bw daily for five days) resulted in increased hepatic microsomal content of cytochrome P450, with induction of several isoforms that exhibit elevated catalytic activities toward pyridine, *N*-nitrosodimethylamine, alcohols and aniline (Kaul & Novak, 1987). Kim *et al.* (1988) confirmed these findings, demonstrating the induction of a high-affinity isozyme [subsequently understood to be CYP2E1] responsible for the production of pyridine *N*-oxide. Treatment of male Sprague-Dawley rats with pyridine as a single intraperitoneal dose of 100 mg/kg bw resulted in moderate induction of hepatic CYP1A1, as judged by inspection of immunoblots (not quantified) (Kim *et al.*, 1991a). Similar results were obtained for renal CYP1A1 and CYP1A2 (Kim *et al.*, 1995). Combined treatment of male Sprague-Dawley rats with pyridine and acetone had over-additive (synergistic) inducing effects on CYP1A1 and CYP1A2 in the liver and CYP1A1 in the lung, where the effect was particularly great. Thus, lung CYP1A1 activity was increased 21-fold by exposure to 20 ppm [65 mg/m^3] pyridine vapour (5–6 h per day for 10 consecutive days), fivefold by oral intake of acetone (7.5% v/v solution in drinking water for 10 consecutive days) and 115.5-fold by the combined treatment (Iba *et al.*, 1993). Other isozymes inducible in rat liver (male Sprague-Dawley) by pyridine treatment are CYP2B1/2B2 and, most notably, CYP2E1 (Kim *et al.*, 1993), while in rabbit liver (male New Zealand White) an increase in CYP2E1 but no increase in CYP2B and only a marginal increase in CYP4B expression was observed (Kim *et al.*, 1991b). In SENCAR mouse skin, topical application of pyridine (300 or 500 mg/kg bw) resulted in increases in CYP1A1, CYP2B1 and CYP3A (Agarwal *et al.*, 1994).

In inhalation experiments in male Fischer 344/N rats, exposure to 5 ppm pyridine for four days (6 h per day) resulted in induction of hepatic CYP2E1 (Hotchkiss *et al.*, 1993). Induction of hepatic CYP2E1 was also observed in male Swiss albino mice and male Sprague-Dawley rats treated daily with 80 mg/kg bw pyridine (given intraperitoneally) for one to three days (Anari *et al.*, 1995). In pyridine-treated male Sprague-Dawley rats (one dose of 100 mg/kg bw, daily for four days), increased CYP2E1 protein was observed in the liver and kidney, while CYP2E1 mRNA was induced only in the kidney, indicating tissue-specific mechanisms of induction (Goasduff *et al.*, 1996). Another enzyme inducible by pyridine is carboxylesterase. Inhalation of 5 ppm pyridine for four days (6 h per day) resulted in increased carboxylesterase immunoreactivity in Bowman's glands and sustentacular cells of the nasal mucosa in male Fischer 344/N rats, 20 hours after the end of exposure (Nikula *et al.*, 1995). In primary cultures of hepatocytes from male Sprague-Dawley rats treated with 25 mM [2 g/L] pyridine for 24 h, the CYP2E1 protein level was increased by about ninefold, and that of CYP2B mRNA and protein by about 30-fold (Zangar *et al.*, 1995).

Acute pyridine treatment (single intraperitoneal dose of 200 mg/kg bw) increased the metabolism of 2-butanol twofold in Sprague-Dawley rat liver microsomes and threefold in rabbit (New Zealand White) liver microsomes (Page & Carlson, 1993). In liver microsomes from pyridine-treated (one intraperitoneal injection of 100 mg/kg bw, daily for four days) male Sprague-Dawley rats, increased oxidative biotransformation of the chlorofluorocarbon 1,2-dichloro-1,1,2-trifluoroethane was found the day after the last injection (Dekant *et al.*, 1995).

In male Sprague-Dawley rats, a single intraperitoneal treatment with pyridine (100 mg/kg bw) enhanced the metabolic activation of carbon tetrachloride 24 h later, leading to increased hepatic expression of the immediate early genes c-*fos* and c-*jun* (Gruebele et al., 1996). Similarly, pyridine treatment (a single intraperitoneal dose of 200 mg/kg bw) of male NSA and CD1 mice resulted in enhanced formation of styrene oxide (*S* enantiomer) from styrene in liver microsomes 18 h after dosing (Carlson, 1997). In agreement with these results, Gadberry *et al.* (1996) reported enhanced hepato- and pneumotoxicity of styrene in male non-Swiss albino mice treated with pyridine. Induction of CYP2E1, after a single intraperitoneal dose of pyridine (200 mg/kg bw) given to male Sprague-Dawley rats, was correlated with increases in *para*-nitrophenol hydroxylation, ethoxyresorufin deethylation and *N*-nitrosodimethylamine metabolism in lung and liver microsomes 24 h after dosing (Carlson & Day, 1992). Treatment of Sprague-Dawley rats by intraperitoneal injection with 100 mg/kg bw pyridine per day for three days led to a threefold increase in testicular microsomal CYP2E1 content and *para*-nitrophenol hydroxylation (Jiang *et al.*, 1998).

Male and female Fischer 344 rats and B6C3F1 mice and male Wistar rats were given drinking water containing 0, 50, 100, 250, 500 or 1000 ppm (mg/L) pyridine for 13 weeks (National Toxicology Program, 1997). Water consumption by female Fischer 344 rats and male Wistar rats exposed to 1000 ppm pyridine was lower than that of control rats. Evidence of anaemia was present in male and female Fischer 344 rats. Exposure to pyridine (500 or 1000 ppm) increased serum alanine aminotransferase and sorbitol dehydrogenase activities and the incidence of centrilobular degeneration, hypertrophy, chronic inflammation and pigmentation in all rats. Spontaneous nephropathy, common in ageing male rats, increased only in male Fischer 344 rats exposed to 500 or 1000 ppm pyridine. The incidence of granular casts and renal tubule hyaline degeneration was increased in male Fischer 344 rats exposed to 500 or 1000 ppm pyridine. Immunohistochemical staining for α_{2u}-globulin was positive in all male rats and negative in female Fischer 344 rats [actual data not reported]. In mice, no treatment-related clinical findings were observed.

Male and female Fischer 344 rats and male Wistar rats were given drinking water containing 0, 100, 200 or 400 ppm (mg/L) pyridine for 103–104 weeks (National Toxicology Program, 1997). Male B6C3F_1 mice were given drinking water containing 0, 250, 500 or 1000 ppm pyridine for 104 weeks and female B6C3F_1 mice 0, 125, 250 or 500 ppm pyridine for 105 weeks. In Fischer 344 rats, the incidence of renal tubule hyperplasia was increased in males exposed to 400 ppm pyridine compared with

controls; the severity of chronic progressive nephropathy was increased slightly in males with increasing exposure concentration, but statistical significance was not indicated; the incidence of mineralization of the stomach in the high-dose males was increased significantly compared with controls; increases in centrilobular cytomegaly and cytoplasmic vacuolization, and pigmentation in the liver were seen in male and females; periportal fibrosis was increased in the liver of males, with an increased incidence of bile duct hyperplasia in females. In male Wistar rats, liver lesions included an increase in the incidence of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation. Spontaneous, age-related chronic progressive nephropathy was moderately severe in control and exposed male Wistar rats and was considered to be the cause of the high mortality in this study. In mice, pyridine increased the incidence of haematopoietic cell proliferation in the spleen and follicular cell hyperplasia in the thyroid gland.

Incubation in 1–20 μM pyridine for 20 min inhibited norepinephrine-induced phasic and tonic contractions in the thoracic aorta, incubated as aortic rings, as well as the endothelium-denuded aorta of Wistar rats (Hsu & Lin-Shiau, 1995). These effects were related to inhibition of the calcium influx normally elicited by norepinephrine.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups of 10 male and 10 female B6C3F_1 mice were exposed to 0, 250, 500 or 1000 ppm (mg/L) pyridine in the drinking-water for 13 weeks. Average daily doses were 0, 50, 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 estrous cycle lengths in females (National Toxicology Program, 1997).

Groups of 10 male and 10 female Fischer 344 rats were exposed to 0, 250, 500 and 1000 ppm pyridine in the 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 estrous cycle length was significantly increased at the highest dose level (National Toxicology Program, 1997).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 5 for references)

Ecotoxicological, including genetic toxicological, data have been reviewed by Jori *et al.* (1983) and the National Toxicology Program (1997).

Pyridine did not induce mutations in *Salmonella typhimurium* with or without metabolic activation, nor in mouse lymphoma L5178Y cells. It also gave negative results in chromosomal aberration assays in two Chinese hamster studies *in vitro* (one without an exogenous metabolic system only) and a mouse bone-marrow test *in vivo*, and in the sister chromatid exchange assay in Chinese hamster cells *in vitro*. The in-vivo mouse micronucleus test was also negative. The cell transformation assay with Syrian hamster embryo cells (without exogenous metabolism only) was negative.

Pyridine lowered the clastogenicity of benzene but not of benzo[*a*]pyrene or cyclophosphamide in the in-vivo mouse bone marrow micronucleus test after oral administration (Harper *et al.*, 1984; Harper & Legator, 1987).

Pyridine induced aneuploidy in *Saccharomyces cerevisiae*, when tested without metabolic activation only.

Three studies have been reported on the sex-linked recessive lethal mutation assay in *Drosophila melanogaster*. An equivocal result was obtained following feeding of pyridine, while a repeat test at a slightly higher concentration was negative; the injection method of treatment also gave a negative result. In another study, administration in the feed gave negative results, while injection gave positive results. The heritable translocation assay was negative in the same laboratory. A further set of experiments in the same laboratory produced negative results for the sex-linked recessive lethal test, although a lower dose for injection was used than in the other experiments.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Pyridine is an organic liquid of disagreeable odour, produced from coal-tar or by chemical synthesis. It is widely used as a solvent and intermediate in the production of piperidine, agricultural chemicals, drugs, dyestuffs, paints, rubber products, polycarbonate resins and textile water-repellents, as well as in laboratories. Occupational exposure may occur through inhalation and dermal contact during its production and its various uses as well as during the processing of oil-shale and at coke-oven works.

Table 5. Genetic and related effects of pyridine

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA1535, TA1537, TA98, reverse mutation	–	–	1000 µg/plate	Haworth *et al*. (1983)
Saccharomyces cerevisiae, aneuploidy	+	NT	9000	Zimmerman *et al*. (1985)
Drosophila melanogaster, sex-linked recessive lethal mutations	?[c]		700 µg/mL; feed	Valencia *et al*. (1985)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		7000 µg/mL; inj	Valencia *et al*. (1985)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		500 µg/mL; feed	National Toxicology Program (2000)
Drosophila melanogaster, sex-linked recessive lethal mutations	+		4300 µg/mL; inj	National Toxicology Program (2000)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		730 µg/mL; feed	Foureman *et al*. (1994)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		500 µg/mL; inj	Foureman *et al*. (1994)
Drosophila melanogaster, heritable translocation test	–		4300 µg/mL; inj	Mason *et al*. (1992)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	–	5000	McGregor *et al*. (1988)
Sister chromatid exchange, Chinese hamster (Don) cells *in vitro*	–	NT	395	Abe & Sasaki (1977)
Sister chromatid exchange, Chinese hamster cells *in vitro*	–	–	5020	National Toxicology Program (2000)
Chromosomal aberrations, Chinese hamster (Don) cells *in vitro*	–	NT	395	Abe & Sasaki (1977)
Chromosomal aberrations, Chinese hamster cells *in vitro*	–	NT	4000	Ishidate & Odashima (1977)
Chromosomal aberrations, Chinese hamster cells *in vitro*	–	–	5000	National Toxicology Program (2000)

Table 5 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cell transformation, Syrian hamster embryo cells, clonal assay	–		5000	Kerckaert *et al*. (1996)
Micronucleus formation, B6C3F_1 mice *in vivo*	–		500 ip × 1	National Toxicology Program (2000)
Chromosomal aberrations, B6C3F_1 mouse bone-marrow cells *in vivo*	–		600 ip × 1	National Toxicology Program (2000)

[a] +, positive; –, negative; ?, inconclusive; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; *Drosophila* tests, ppm in feed; inj, injection
[c] Repeat test negative at 729 ppm

It is rarely detected in ambient air or drinking water but is frequently found in indoor air. It is present in cigarette smoke and in the volatile components of certain foodstuffs.

5.2 Human carcinogenicity data

One mortality study of workers at a 4,4′-bipyridyl manufacturing plant using pyridine as a starting material showed a small non-significant excess of lung cancer mortality. This excess could not be attributed to specific chemical exposures within the plant, and it was not clear if the risk associated with pyridine exposure was specifically assessed.

5.3 Animal carcinogenicity data

Pyridine was tested for carcinogenicity by oral administration in the drinking-water in one experiment in mice and in two experiments in rats and by subcutaneous injection in one experiment in rats. In male and female mice, it increased incidences of hepatocellular carcinomas and hepatoblastomas. In male Fischer 344 rats, it increased the incidence of renal tubule adenomas but not in male Wistar rats. No increase in tumour incidence at any site was observed in rats following subcutaneous injection of pyridine for one year and a subsequent observation period of six months.

In two studies with genetically modified mice, there was no treatment-related increase in the incidence of tumours.

5.4 Other relevant data

Pyridine is well absorbed from the gastrointestinal tract in mammals, and undergoes extensive metabolism by *C*- and *N*-oxidation and by *N*-methylation, giving the quaternary ion *N*-methylpyridinium.

In humans, acute pyridine intoxication affects the central nervous system, leading to dizziness, headache, nausea and anorexia. There is one case report of lethality after a high dose. Further symptoms include abdominal pain and pulmonary congestion. Pyridine was hepatotoxic in Fischer 344 and Wistar rats and caused an increase in granular casts and renal tubule hyaline degeneration in male Fischer 344 rats. Inhalation of pyridine can cause necrotic damage of the nasal epithelium. In rats and rabbits, pyridine is an inducer of CYP2E1 in the liver and kidney.

No data on reproductive and developmental effects in humans were available.

Exposure to pyridine in drinking-water led to reduction of sperm motility at all dose levels in mice and increased estrous cycle length at the highest dose level in rats.

Apart from positive responses in the sex-linked recessive lethal assay in *Drosophila melanogaster* and for aneuploidy in a fungal system, all tests, covering a range of end-points, for genetic toxicology of pyridine gave negative results.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of pyridine.

There is *limited evidence* in experimental animals for the carcinogenicity of pyridine.

Overall evaluation

Pyridine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

Abe, S. & Sasaki, M. (1977) Chromosome aberrations and sister chromatid exchanges in Chinese hamster cells exposed to various chemicals. *J. natl Cancer Inst.*, **58**, 1635–1641

Aeschbacher, H.U., Wolleb, U., Löliger, J., Spadone, J.C. & Liardon, R (1989) Contribution of coffee aroma constituents to the mutagenicity of coffee. *Food chem. Toxicol*., **27**, 227–231

Agarwal, R., Jugert, F.K., Khan, S.G., Bickers, D.R., Merk, H.F. & Mukhtar, H. (1994) Evidence for multiple inducible cytochrome P450 isozymes in SENCAR mouse skin by pyridine. *Biochem. biophys. Res. Comm.*, **199**, 1400–1406

Agency for Toxic Substances and Disease Registry (1992) *Toxicological Profile for Pyridine* (TP-91/24), Atlanta, GA, Department of Health and Human Services, Public Health Service

American Conference of Governmental Industrial Hygienists (1999) *TLVs and other Occupational Exposure Values—1999* [CD-ROM], Cincinnati, OH, ACGIH

Anari, M.R., Cribb, A.E. & Renton, K.W. (1995) The duration of induction and species influences the downregulation of cytochrome P450 by the interferon inducer polyinosinic acid-polycytidylic acid. *Drug Metab. Dispos*., **23**, 536–541

Apol, A.G. (1982) *Gerlinger Casting Corporation, Salem, Oregon* (Health Hazard Evaluation Report No. HETA 81-133-1110), Cincinnati, OH, Department of Health and Human Services, Hazard Evaluations and Technical Assistance Branch, National Institute for Occupational Safety and Health

Baxter, J.H. (1947) Hepatic and renal injury with calcium deposits and cirrhosis produced in rats by pyridine. *Am. J. Pathol*., **24**, 503–525

Bienik, G., Cisowska, G., Lusiak, T. & Siwek, A. (1993) [Estimation of exposure to benzene in coke plant workers]. *Med. Prac.*, **6**, 579–586 (in Polish)

Brunneman, K.D., Cox, J.E. & Kagan, M.R. (1991) Analysis of selected environmental tobacco smoke components in indoor air by thermal absorption-GC-MS. *Proc. CORESTA 1990* (cited in Agency for Toxic Substances and Disease Registry, 1992)

Budavari, S., ed. (1998) *The Merck Index*, 12th Ed., Version 12:2 [CD-ROM], Whitehouse Station, NJ, Merck & Co.

Burdick & Jackson (1997) *Burdick & Jackson Solvent Guide*, Muskegon, MI, pp. 240–243

Burdock, G.A. (1995) *Fenaroli's Handbook of Flavor Ingredients*, Volume II, 3rd Ed., Boca Raton, CRC Press

Carlson, G.P. (1997) Effects of inducers and inhibitors on the microsomal metabolism of styrene to styrene oxide in mice. *J. Toxicol. environ. Health*, **51**, 477–488

Carlson, G.P. & Day, B.J. (1992) Induction by pyridine of cytochrome P450IIE1 and xenobiotic metabolism in rat lung and liver. *Pharmacology*, **44**, 117–123

Chemical Information Services (1999) *Directory of World Chemical Producers*, Version 99.1.0 [CD-ROM], Dallas, TX

Curvall, M., Enzell, C.R. & Pettersson, B. (1984) An evaluation of the utility of four in vitro short term tests for predicting the cytotoxicity of individual compounds derived from tobacco smoke. *Cell Biol. Toxicol*., **1**, 173–193

Damani, L.A., Crooks, P.A., Shaker, M.S., Caldwell, J., D'Souza, J. & Smith, R.L. (1982) Species differences in the metabolic *C*- and *N*-oxidation, and *N*-methylation of [^{14}C]pyridine *in vivo*. *Xenobiotica*, **12**, 527–534

Dekant, W., Assmann, M. & Urban, G. (1995) The role of cytochrome P450 2E1 in the species-dependent biotransformation of 1,2-dichloro-1,1,2-trifluoroethane in rats and mice. *Toxicol. appl. Pharmacol*., **135**, 200–207

Deutsche Forschungsgemeinschaft (1999) *List of MAK and BAT Values 1999* (Report No. 35), Weinheim, Wiley-VCH, p. 92

Dobson, K.R., Stephenson, M., Greenfield, R.F. & Bell, P.R.F. (1985) Identification and treatability of organics in oil shale retort water. *Water Res*., **19**, 849–856

Dreibelbis, W.G., Ealy, J.A. & Porter, W.E. (1982) Industrial hygiene monitoring for evaluation of employee exposure and control measures in coal conversion program at Oak Ridge National Laboratory. In: Cooke, M. & Dennis, A.J., eds, *Polycyclic Aromatic Hydrocarbons: Mechanisms, Methods and Metabolism, Proceedings of the Eight International Symposium*, Columbus, OH, Battelle Press, pp. 351–361

D'Souza, J., Caldwell, J. & Smith, R.L. (1980) Species differences in the *N*-methylation and quaternization of [^{14}C]pyridine. *Xenobiotica*, **10**, 151–157

Dumont, J.-P. & Adda, J. (1978) Occurrence of sesquiterpenes in mountain cheese volatiles. *J. agric. Food Chem*., **26**, 364–367

Dutch Ministry of Social Affairs and Employment (1993) *Health-based Recommended Occupational Exposure Limit for Pyridine* (Dutch Expert Committed on Occupational Standards), The Hague, Sdu Uitgeverij

Eatough, D.J., Benner, C.L., Bayona, J.M., Richards, G., Lamb, J.D., Lee, M.L., Lewis, E.A. & Hansen, L.D. (1989) Chemical composition of environmental tobacco smoke. *Environ. Sci. Technol*., **23**, 679–687

Eller, P.M., ed. (1994) *NIOSH Manual of Analytical Methods* (DHHS (NIOSH) Publ. No. 94-113), 4th Ed., Cincinnati, OH, United States National Institute for Occupational Safety and Health [Method 1613]

Environmental Protection Agency (1995) *Method 1665. Semi-volatile Organic Compounds Specific to the Pharmaceutical Manufacturing Industry by Isotope Dilution GC/MS*, Washington DC

Environmental Protection Agency (1996a) *Method 8015B – Nonhalogenated Organics Using GC/FID*, Washington DC

Environmental Protection Agency (1996b) Method 8260B. Volatile organic compounds by gas chromatography/mass spectrometry (GC/MS) [Rev. 2]. In: *Test Methods for Evaluating Solid Waste–Physical/Chemical Method* 9US EPA No. SW 846), Washington DC, Office of Solid Waste

Environmental Protection Agency (1996c) *1994 Toxic Release Inventory* (EPA 745-R-96-002), Washington DC

Environmental Protection Agency (1999) *1997 Toxics Release Inventory* (EPA 745-F-99-001), Washington DC, Office of Pollution Prevention and Toxics

Felten, R.K., DeNicola, D.B. & Carlson, G.P. (1998) Minimal effects of acrylonitrile on pulmonary and hepatic cell injury enzymes in rats with induced cytochrome P450. *Drug chem. Toxicol*., **21**, 181–194

Finnish Ministry of Social Affairs and Health (1998) *Finnish Occupational Exposure Limits 1998. Concentrations Known to be Harmful* [http://www.occuphealth.fi]

Food and Drug Administration (1999) Synthetic flavoring substances and adjuvants. *US Code Fed. Regul*., **Title 21**, chap. 1, Part 172.515, pp. 52-59

Foureman, P., Mason, J.M., Valencia, R. & Zimmering, S. (1994) Chemical mutagenesis testing in *Drosophila*. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ. mol. Mutag*., **23**, 208–227

Gadberry, M.G., DeNicola, D.B. & Carlson, G.P. (1996) Pneumotoxicity and hepatotoxicity of styrene and styrene oxide. *J. Toxicol. environ. Health*, **48**, 273–294

Goasduff, T., Bellec, G., Amet, Y., Dreano, Y., Menez, J.F. & Berthou, F. (1996) P450 2E1 expression in liver, kidney, and lung of rats treated with single or combined inducers. *Alcohol*, **3**, 301–308

Gruebele, A., Zawaski, K., Kaplan, D. & Novak, R.F. (1996) Cytochrome P4502E1- and cytochrome P4502B1/2B2-catalyzed carbon tetrachloride metabolism. Effects on signal transduction as demonstrated by altered immediate-early (c-fos and c-jun) gene expression and nuclear AP-1 and NF-κB transcription factor levels. *Drug Metab. Dispos*., **24**, 15–22

Hansch, C., Leo, A. & Hoekman, D. (1995) *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*, Washington DC, American Chemical Society, p. 12

Harper, B.L. & Legator, M.S. (1987) Pyridine prevents the clastogenicity of benzene but not of benzo[*a*]pyrene or cyclophosphamide. *Mutat. Res.*, **179**, 23–31

Harper, B.L., Sadagopa Ramanujam, V.M., Gad-el-Karim, M.M. & Legator, M.S. (1984) The influence of simple aromatics on benzene clastogenicity. *Mutat. Res.*, **128**, 105–114

Hartle, R. & Erhenberg, R. (1985) *Packard Electric, Warren, Ohio* (Health Hazard Evaluation Report No. HETA 84-406-1617), Cincinnati, OH, Department of Health and Human Services, Hazard Evaluations and Technical Assistance Branch, National Institute for Occupational Safety and Health

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. *Environ. Mutag.*, **Suppl. 1**, 3–142

Hawthorne, S.B. & Sievers, R.E. (1984) Emissions of organic air pollutants from shale oil waste waters. *Environ. Sci. Technol*., **18**, 483–490

Ho, C.-T., Lee, K.N. & Jin, Q.Z. (1983) Isolation and identification of volatile flavor compounds in fried bacon. *J. agric. Food Chem*., **31**, 336–342

Hotchkiss, J.A., Kim, S.G., Novak, R.F. & Dahl, A.R. (1993) Enhanced hepatic expression of P450IIE1 following inhalation exposure to pyridine. *Toxicol. appl. Pharmacol*., **118**, 98–104

Hsu, K.-S. & Lin-Shiau, S.-Y. (1995) Relaxation of rat thoracic aorta induced by pyridine. *Eur. J. Pharmacol*., **292**, 265–270

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 38, *Tobacco Smoking*, Lyon, IARC*Press*, p. 110

Iba, M.M., Bennett, S., Storch, A., Ghosal A. & Thomas, P.E. (1993) Synergistic induction of rat microsomal CYP1A1 and CYP1A2 by acetone in combination with pyridine. *Cancer Lett.*, **74**, 69–74

Ishidate, M., Jr & Odashima, S. (1977) Chromosome tests with 134 compounds on Chinese hamster cells in vitro—a screening for chemical carcinogens. *Mutat. Res.*, **48**, 337–354

Izmerov, N. F. (1984) *Pyridine* (IRPTC Scientific Reviews of Soviet Literature on Toxicity and Hazards of Chemicals), United Nations Environmental Programme, Moscow, Centre of International Projects, GKNT

Jiang, Y., Kuo, C.-L., Pernecky, S.J. & Piper, W.N. (1998) The detection of cytochrome P450 2E1 and its catalytic activity in rat testis. *Biochem. biophys. Res. Commun*., **246**, 578–583

Jori, A., Calamari, D., Cattabeni, F., Di Domenico, A., Galli, C.L., Galli, E. & Silano, V. (1983) Ecotoxicological profile of pyridine. *Ecotoxicol. environ. Saf*., **7**, 251–275

Junk, G. & Ford, C. (1980) A review of organic emissions from selected combustion processes. *Chemosphere*, **9**, 187–230

Kaul, K.L. & Novak, R.F. (1987) Inhibition and induction of rabbit liver microsomal cytochrome P-450 by pyridine. *J. Pharmacol. exp. Ther*., **243**, 384–390

Kerckaert, G.A., Brauninger, R., LeBoeuf, R.A. & Isfort, R.J. (1996) Use of the Syrian hamster cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ. Health Perspect.*, **104** (Suppl. 5), 1075–1084

Kim, S.G., Williams, D.E., Schuetz, E.G., Guzelian, P.S. & Novak, R.F. (1988) Pyridine induction of cytochrome P-450 in the rat: role of P-450j (alcohol-inducible form) in pyridine N-oxidation. *J. Pharmacol. exp. Ther*., **246**, 1175–1182

Kim, S.G., Reddy, S.L., States, J.C. & Novak, R.F. (1991a) Pyridine effects on expression and molecular regulation of the cytochrome P450IA gene subfamily. *Mol. Pharmacol*., **40**, 52–57

Kim, S.G., Philpot, R.M. & Novak, R.F. (1991b) Pyridine effects on P450IIE1, IIB and IVB expression in rabbit liver: characterization of high- and low-affinity pyridine N-oxygenases. *J. Pharmacol. environ. Ther*., **259**, 470–477

Kim, H., Putt, D., Reddy, S., Hollenberg, P.F. & Novak, R.F. (1993) Enhanced expression of rat hepatic CYP2B1/2B2 and 2E1 by pyridine: differential induction kinetics and molecular basis of expression. *J. Pharmacol. exp. Ther*., **267**, 927–936

Kim, H., Reddy, S. & Novak, R.F. (1995) 3-Methylcholanthrene and pyridine effects on CYP1A1 and CYP1A2 expression in rat renal tissue. *Drug Metab. Dispos*., **23**, 818–824

Leenheer, J.A. & Stuber, H.A. (1981) Migration through soil of organic solutes in an oil-shale process water. *Environ. Sci. Technol*., **15**, 1467–1475

Lide, D.R. & Milne, G.W.A. (1996) *Properties of Organic Compounds*, Version 5.0 [CD-ROM], Boca Raton, FL, CRC Press

Liu, S.-M. & Kuo, C.-L. (1997) Anaerobic biotransformation of pyridine in estuarine sediments. *Chemosphere*, **35**, 2255–2268

Mašek, V. (1981) [Determination of pyridine bases present in the air of workplaces in metallurgical plants.] *Staub-Reinhalt. Luft*, **41**, 26–28 (in German)

Mason, M.M., Cate, C.C. & Baker, J. (1971) Toxicology and carcinogenesis of various chemicals used in the preparation of vaccines. *Clin. Toxicol*., **4**, 185–204

Mason, J.M., Valencia, R. & Zimmering, S. (1992) Chemical mutagenesis testing in *Drosophila*: VIII. Reexamination of equivocal results. *Environ. mol. Mutag.*, **19**, 227–234

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D. & Caspary, W.J. (1988) Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay II: 18 coded chemicals. *Environ. mol. Mutag.*, **11**, 91–118

National Toxicology Program (2000) *Toxicology and Carcinogenesis Studies of Pyridine (CAS No. 110-86-1) in F344/N Rats, Wistar Rats and B6C3F1 Mice (Drinking Water Studies)* (Technical Report No. 470), Research Triangle Park, NC, Department of Health and Human Services

Nikula, K.J. & Lewis, J.L. (1994) Olfactory mucosal lesions in F344 rats following inhalation exposure to pyridine at threshold limit value concentrations. *Fundam. appl. Toxicol*., **23**, 510–517

Nikula, K.J., Novak, R.F., Chang, I.Y., Dahl, A.R., Kracko, D.A., Zangar, R.C., Kim, S.G. & Lewis, J.L. (1995) Induction of nasal carboxylesterase in F344 rats following inhalation exposure to pyridine. *Drug Metab. Dispos*., **23**, 529–535

NOES (1999) *National Occupational Exposure Survey 1981–83*. Unpublished data as of July 1999. Cincinnati, OH, Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occuptional Safety and Health

Occupational Safety and Health Administration (1999) Air contaminants. *US Code. Fed. Regul*., **Title 29**, Part 1910, Subpart 1910.1000, pp. 7–19

Otson, R., Fellin, P. & Tran, Q. (1994) VOCs in representative Canadian residences. *Atmos. Environ*., **28**, 3563–3569

Paddle, G.M., Osborn, A.J. & Parker G.D.J. (1991) Mortality of employees in plants manufacturing 4,4′-bipyridyl. *Scand. J. Work. Environ. Health*, **17**, 175–178

Page, D.A. & Carlson, G.P. (1993) Effect of pyridine on the hepatic and pulmonary metabolism of 2-butanol in rat and rabbit. *J. Toxicol. environ. Health*, **38**, 369–379

Pellizzari, E.D., Castillo, N.P. & Willis, S. (1979) Identification of organic components in aqueous effluents from energy-related processes. In: Van Hall, ed., *Measurements of Organic Pollutants in Water and Wastewater (ASTM STP, 686)*, Philadelphia, PA, American Society for Testing and Materials, pp. 256–274

Sadtler Research Laboratories (1980) *Sadtler Standard Spectra, 1980 Cumulative Index*, Philadelphia, PA

Santodonato, J., Bosch, S., Meylan, W., Becker, J. & Neal, M. (1985) *Monograph on Human Exposure to Chemicals in the Workplace: Pyridine* (Report No. SRC-TR-84-1119), Syracuse, New York, Syracuse Research Corporation, Center for Chemical Hazard Assessment

Schmeltz, I. & Hoffmann, D. (1977) Nitrogen-containing compounds in tobacco and tobacco smoke. *Chem. Rev.*, **77**, 295–311

Scriven, E.F.V., Toomey, J.E., Jr & Murugan, R. (1996) Pyridine and pyridine derivatives. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 20, New York, John Wiley, pp. 641–679

Shah, J.J. & Heyerdahl, E.K. (1988) *National Ambient Volatile Organic Compounds (VOCs) Data Base Update*. Report by Nero and Associates, Inc., Portland, OR, to Environmental Protection Agency, Atmospheric Sciences Research Laboratory, Research Triangle Park, NC. EPA 600/3-88/010(A) [cited in Agency for Toxic Substances and Disease Registry, 1992]

Shibamoto, T., Kamiya, Y. & Mihara, S. (1981) Isolation and identification of volatile compounds in cooked meat: sukiyaki. *J. agric. Food Chem.*, **29**, 57–63

Shimizu, S., Watanabe, N., Kataoka, T., Shoji, T., Abe, N., Morishita, S. & Ichimura, H. (1993) Pyridine and pyridine derivatives. In: Elvers, B., Hawkins, S., Russey, W. & Schulz, G., eds, *Ullmann's Encyclopedia of Chemical Technology*, 5th rev. Ed., Vol. A22, New York, VCH Publishers, pp. 399–430

Sims, G.K. & O'Loughlin, E.J. (1989) Degradation of pyridines in the environment. *CRC crit. Rev. environ. Contam.*, **19**, 309–340

Smith, J.N. (1953) Studies in detoxication. 53. The glucuronic acid conjugation of hydroxyquinolines and hydroxypyridines in the rabbit. *Biochem. J.*, **55**, 156–160

Spalding, J.W., French, J.E., Stasiewicz, S., Furedi-Machacek, M., Conner, F., Tice, R.R. & Tennant, R.W. (2000) Responses of transgenic mouse lines $p53^{+/-}$ and Tg.AC to agents tested in conventional carcinogenicity bioassays. *Toxicol. Sci.*, **53**, 213–223

Stuermer, D.H., Ng, D.J. & Morris, C.J. (1982) Organic contaminants in groundwater near an underground coal gasification site in northeastern Wyoming. *Environ. Sci. Technol.*, **16**, 582–587

Tang, J., Jin, Q.Z., Shen, G.-H., Ho, C.-T. & Cheng, S.S. (1983) Isolation and identification of volatile compounds from fried chicken. *J. agric. Food Chem.*, **31**, 1287–1292

Tolando, R., Ferrara, R., Eldirdiri, N.I., Albores, A., King, L.J. & Manno, M. (1996) Reductive activation of 1,1-dichloro-1-fluoroethane (HCFC-141b) by phenobarbital- and pyridine-induced rat liver microsomal cytochrome P450. *Xenobiotica*, **4**, 425–435

Valencia, R., Mason, J.M., Woodruff, R.C. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ. Mutag.*, **7**, 325–348

Verschueren, K. (1996) *Handbook of Environmental Data on Organic Chemicals*, 3rd Ed., New York, Van Nostrand Reinhold, pp. 1600–1603

Vitzthum, O., Werkhoff, P. & Hubert, P. (1975) New volatile constituents of black tea aroma. *J. agric. Food Chem.*, **23**, 999–1003

Walsh, K.M. & Poteracki, J. (1994) Spontaneous neoplasms in control Wistar rats. *Fundam. appl. Toxicol.*, **22**, 65–72

Zangar, R.C., Woodcroft, K.J., Kocarek, T.A. & Novak, R.F. (1995) Xenobiotic-enhanced expression of cytochrome P450 2E1 and 2B1/2B2 in primary cultured rat hepatocytes. *Drug Metab. Dispos.*, **23**, 681–687

Zhu, S., Bell, P.R.F. & Greenfield, P.F. (1988) Adsorption of pyridine onto spent Rundle oil shale in dilute aqueous solution. *Water Res.*, **22**, 1331–1337

Zimmermann, F.K., Gröschel-Stewart, U., Scheel, I. & Resnick, M.A. (1985) Genetic change may be caused by interference with protein-protein interactions. *Mutat. Res.*, **150**, 203–210