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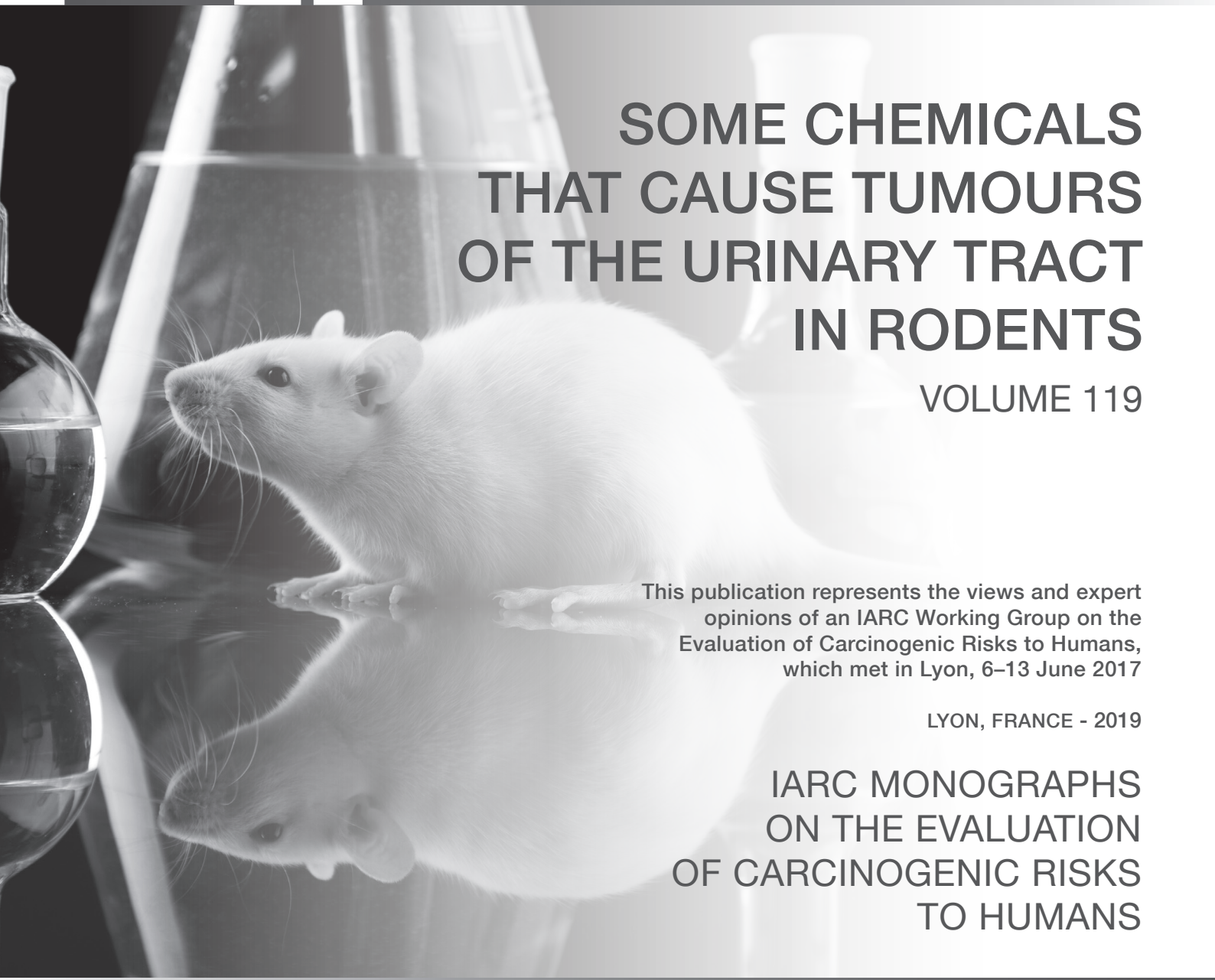

SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

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International Agency for Research on Cancer

World Health Organization

PYRIDINE

1. Exposure Data

Pyridine was considered by the Working Group in 2000 (IARC, 2000). New data have become available since that time, and these have been incorporated and taken into consideration in the present evaluation.

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 110-86-1

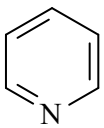
EC/List No.: 203-809-9

Chem. Abstr. Serv. name: Pyridine

IUPAC systematic name: Pyridine

Synonyms: Azabenzene; azine (IARC, 2000)

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: C_5H_5N

Relative molecular mass: 79.10

1.1.3 Chemical and physical properties

Description: Colourless liquid with a characteristic, disagreeable odour (IARC, 2000; IPCS, 2000), also reported as colourless to yellow liquid with a nauseating, fish-like odour (NIOSH, 2016)

Boiling point: 115 °C (IPCS, 2000)

Melting point: −42 °C (IPCS, 2000)

Density: 0.9819 g/cm^3 at 20 °C (Lide & Milne, 1996)

Solubility: Miscible with water, acetone, benzene, chloroform, diethyl ether, and ethanol (Lide & Milne, 1996); solubility in water, 1000 g/L at 20 °C (ECHA, 2017)

Volatility: Vapour pressure, 2.67 kPa at 20 °C (ECHA, 2017)

Relative vapour density: 2.73 (air = 1); relative density of the vapour/air mixture at 20 °C, 1.03 (IPCS, 2000)

Stability: Flammable; lower flammability limit, 1.8%; upper flammability limit, 12.4% (IPCS, 2000; ECHA, 2017)

Flash point: 20 °C (close cup) (IPCS, 2000; ECHA, 2017)

Auto-ignition temperature: 482 °C (IPCS, 2000); 900 °C at standard atmospheric pressure of 101.3 kPa (ECHA, 2017)

Specific gravity: 0.98 at 20 °C (NIOSH, 2016)

Ionization potential: 9.27 eV (NIOSH, 2016)

Octanol/water partition coefficient (P): log K_{ow}, 0.65 (IPCS, 2000)

pH: 8.81 (ECHA, 2017)

Odour threshold: 0.2 ppm (0.65 mg/m^3) (SCOEL, 2004)

Conversion factor: 1 ppm = 3.24 mg/m^3 (NIOSH, 2016)

Impurities: Specifications of pyridine vary according to country but are usually of > 99.8% purity by gas chromatographic analysis (Shimizu et al., 2012)

1.2 Production and use

1.2.1 Production process

Historically, pyridine was extracted from coal tar or obtained as a by-product of coal gasification. The process was labour-consuming and inefficient: coal tar contains only about 0.1% pyridine, and therefore a multistage purification was required, which further reduced the output (Gossauer, 2006).

Today, most pyridine is produced synthetically using various reactions. The Tchichibabin synthesis, which is a condensation reaction of aldehydes with ammonia (Tchichibabin, 1924), is especially suitable for mass production. The reaction of acetaldehyde and formaldehyde with ammonia is one of the most widely used for pyridine production. It is usually carried out at 350–550 °C and a space velocity of 500–1000 h^{-1} in the presence of a solid acid catalyst (e.g. silica–alumina). Alkylpyridines of low commercial value, obtained as by-products of pyridine base synthesis, can be converted into useful pyridine bases by dealkylation. These and other syntheses are described in detail by Shimizu et al. (2012).

1.2.2 Production volume

Major companies producing pyridine are located in China, India, and the USA (Murugan & Scriven, 2013). A directory of chemicals, chemical suppliers, and producers lists 28 international suppliers and manufacturers of pyridine: 13 of them are in China, 6 in Germany, 5 in the USA, 2 in Belgium, 1 in Sweden, and 1 in Switzerland (BuyersGuideChem, 2018). Another directory listed 37 manufacturers of pyridine, including 18 in the USA, 5 in the United Kingdom, 3 in China, 3 in Japan, 2 in Germany, 2 in Hong Kong Special Administrative Region, 1 in Belgium, 1 in Canada, 1 in Mexico, and 1 in Switzerland (Chemical Sources International, 2017).

According to the European Chemicals Agency (ECHA) database, pyridine is registered under a 1000–10 000 tonnes/year usage with seven active registrants and/or suppliers in Europe (ECHA, 2017).

Pyridine appears on the 2007 Organisation for Economic Co-operation and Development (OECD) list of high production volume chemicals (OECD, 2009), which contains those chemicals which are produced or imported at levels greater than 1000 tonnes/year in at least one member country and/or region. [The OECD has 35 member countries, including many of the world's most industrialized countries in the Asia-Pacific region, Europe, and North and South America.] Global domestic pyridine capacity reached 145 000 tonnes in 2011, 60% (87 000 tonnes) of which was accounted for by China (CCPIA, 2012).

1.2.3 Use

Pyridine as a solvent is used in organic chemistry and in industry. Pyridine is used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides, herbicides, and fungicides

(NTP, 2000). It is also used in the production of piperidine and as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellents, and flavouring agents in food (NTP, 2000). Agricultural chemicals, mainly the non-selective contact herbicide paraquat, account for most consumption of pyridine (SCOEL, 2004; IHS Markit, 2014).

1.3 Analytical methods

Methods of detection and quantification of pyridine are reported in Table 1.1. The methods used to evaluate pyridine concentrations in different media such as air, water, soil, or food are based on gas chromatography with flame ionization detection, nitrogen–phosphorus detection, or mass spectrometry.

No methods for biological matrix are available for this compound.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

Pyridine is reported to occur naturally in wood oil, in the leaves and roots of *Atropa belladonna*, and in other plants, for example, coffee and tobacco (Furia & Bellanca, 1975). Pyridine can be formed from the breakdown of many natural materials in the environment. Moreover, due to its variety of applications, pyridine can be released to the environment since it presents high volatility and evaporates into the air very easily. If pyridine is released into the air, it may take several months to years to break down into other compounds. Pyridine also mixes very easily with water. If it is released into water or soil, it may break down in a few days to a few months (ATSDR, 1992).

In 2015, according to the United States Environmental Protection Agency Toxic Release Inventory (TRI), about 529 200 pounds [240 tonnes] of pyridine were released into the environment through on- and offsite disposal or other releases. Onsite air emissions accounted for 38 000 pounds [17.2 tonnes, 7% of total releases]; of this total, land [soil] releases represented 92% of total releases, and offsite disposal or other represented 1% (EPA-TRI, 2018).

The fate of pyridine in the environment is a function of both abiotic and biotic processes, including photochemical transformations, volatilization, complexation, surface attenuation, transport, and biological degradation. Pyridine and several pyridine derivatives such as hydroxypyridines and pyridinecarboxylic acids can be degraded in soil by bacteria. Data suggest that pyridine and some substituted pyridines are degraded via different mechanisms, possibly involving initial reductive steps and lacking hydroxylated intermediates ubiquitous in the metabolism of other aromatic compounds. Perhaps least understood are the mechanisms for catabolism of alkyl- and chloropyridines, two of the most important classes of pyridine derivatives detected in environmental samples (Sims et al., 1989).

Pyridine and its derivatives can be formed in foods from carbonyl compounds derived from lipids (or reducing sugars) and ammonia released from amino acids (Maga, 1981; Kim et al., 1996). However, other pathways are described for pyridine formation in foods; for example, during coffee roasting trigonelline is degraded, producing a variety of volatile compounds including pyridines (46%), pyrrols (3%), and pyrazines (Farah, 2012). Little attention has been given to pyridine derivatives, although many of them have been found in a large number of foods. Moreover, many food flavour additives are complex mixtures that contain pyridine or pyridine-ring structures that may decompose into pyridine (WHO, 2012) (see also Section 1.5).

Table 1.1 Methods of detection and quantification of pyridine

Media	Method	Technique	Target concentrations	Remarks
Air	NIOSH 1613, issue 2 (NIOSH, 1994)	GC-FID	Estimated LOD, 0.02 mg per sample; working range, 1–14 ppm (3–45 mg/m^3) for 100-L air sample	Replaces method S161 of 1977
	IRSST 199-1 (IRSST, 2012)	GC-NPD	Minimum reported value, 4 µg	
	OSHA PV2295 (OSHA, 1991)	GC-FID	5 ppm (15 mg/m^3)	As of December 1991, the method was partially validated and presented for information and trial use only
Soil and water	EPA 8260B-3 Revision 2 (EPA, 1996)	GC-MS	EQL: ~5 µg/kg for soil samples (wet weight), ~0.5 mg/kg for wastes (wet weight), and ~5 µg/L for groundwater samples	Generic method; adequate for preparation technique 5031 (injection of sample concentrated by azeotropic distillation) and direct injection
	(Peters & van Renesse von Duivenbode, 1994)	GC-MS	Detection limit is 0.01 mg/kg for soil samples and 0.2 µg/L for water samples	Minimum weight for soil samples, 20 g; minimum volume for water samples, 500 mL
Waste water in pharmaceutical manufacturing	EPA Method 1665 (EPA, 1995)	GC-MS	Minimum level, 5 µg/L	Accuracy, 7–12 µg/L
Mainstream cigarette smoke	Saha et al. (2010)	RP-HPLC, ESI-MS/MS	Limit of detection, 1.74–14.32 ng per cigarette	The yields measured by standard machine-smoking tests are misleading and have little value in the assessment of human exposure (IARC, 2004)
Foods and beverages				
Fried bacon, fried pork loin	Timón et al. (2004)	GC-MS	0.0567 ± 0.0072 µg/kg	Pyridine found in headspace volatiles of fried bacon expressed as µg/kg of sample
Coffee	Amanpour & Selli (2016)	GC-FID, GC-MS	3904–4360 µg/kg	Liquid–liquid extraction with dichloromethane; mean concentrations of coffee obtained from two different brewing methods were analysed; limit of detection not reported

EPA, Environmental Protection Agency; EQL, estimated quantitation limits; ESI, electrospray ionization; FID, flame ionization detection; GC, gas chromatography; HPLC, high-performance liquid chromatography; IRSST, Institut de recherche Robert-Sauvé en santé et en sécurité du travail; LOD, limit of detection; MS, mass spectrometry; NIOSH, National Institute for Occupational Safety and Health; NPD, nitrogen-phosphorous detection; OSHA, Occupational Safety and Health Administration; ppm, parts per million; RP, reverse-phased

1.4.2 Exposure in the general population

Humans may be exposed to pyridine by ingestion, inhalation, or dermal contact; food and tobacco smoke are thought to be the major sources of exposure to pyridine for the general population (Maga, 1981; Eatough et al., 1989; IARC, 2000). Pyridine was rarely detected in ambient rural or urban air in the 1980s in the USA, except in the vicinity of industrial or waste-treatment facilities (ATSDR, 1992). Exposure to low concentrations of pyridine may also occur by ingesting pyridine-contaminated water. Pyridine was rarely detected in rivers or other natural waters in the 1970s and 1980s in the USA (ATSDR, 1992). Since the publication of the previous *Monograph* (IARC, 2000), no further data on pyridine in food or water were available to the Working Group.

Pyridine was identified in cigarette smoke constituents (Eatough et al., 1989; Kulshreshtha & Moldoveanu, 2003; Saha et al., 2010; Wright, 2015). Pyridine may be produced from nicotine degradation, and its quantity in mainstream cigarette smoke has been reported to range from 3 to 28 µg per cigarette (Kulshreshtha & Moldoveanu, 2003; IARC, 2004; Herrington & Myers, 2015; Kibet et al., 2016). In 30 brands of cigarettes sold in China, the average pyridine yield was 17 µg per cigarette (standard deviation, 3.9 µg per cigarette) (Xie et al., 2012). The yields measured by standard machine-smoking tests are misleading and have little value in the assessment of human exposure. Mean concentrations of pyridine in second-hand tobacco smoke in different studies ranged from 6.5 to 23.8 µg/m^3 (IARC, 2004). Pyridine was detected but not quantified in an electronic cigarette (e-cigarette) (Margham et al., 2016). Analysis of e-cigarette solutions identified several pyridine derivatives, three of which were also identified in resultant aerosols (Herrington & Myers, 2015).

EPA (1978) reported that total pyridine ingested in the USA is estimated at about 500 mg/year per person, mainly from food. Pyridine was detected among the volatile components of several foods, including fried chicken (Jayasena et al., 2013), fried bacon (Timón et al., 2004), French fries (van Loon et al., 2005), corn tortilla chips (Buttery & Ling, 1998), roasted duck or goose (Baruth & Ternes, 2011), tea (Ho et al., 2015), and mango fruit (Pino et al., 2005). Pyridine is also a coffee aroma constituent (Farah, 2012; Petisca et al., 2013; Amanpour & Selli, 2016; Lee et al., 2017). Few articles describe pyridine content in foods; most of the above-mentioned articles describe only pyridine identification. The concentration of pyridine is 4360 µg/kg in French press coffee and 3904 µg/kg in Turkish coffee (Amanpour & Selli, 2016). Pyridine is also found in corn tortilla chips at the approximate concentration of 30 µg/kg (Buttery & Ling, 1998), fried bacon at 0.06 µg/kg (Timón et al., 2004), and mango fruit from non-detectable amounts to 80 µg/kg (Pino et al., 2005).

The assessment of 33 derivatives of pyridine, pyrrole, indole, and quinoline was undertaken by EFSA (2008). The daily per capita intakes for these flavourings were estimated on the basis of the annual volumes of production reported. More than 50% of the total annual volume of production for the 33 candidate substances is accounted for by the following three flavourings: 4-methylpyridine, 1-methylpyrrole, and 2-methylpyridine. The estimated daily per capita intakes of these three substances from use as flavourings are 0.73, 0.3, and 0.21 µg, respectively. The daily per capita intakes for each of the 30 remaining substances (including pyridine derivatives) are less than 0.2 µg. [The Working Group noted that this assessment was only for pyridine derivatives, which could degrade to pyridine in the food preparation or metabolize to pyridine in the body.]

1.4.3 Occupational exposure

Pyridine is produced in closed and open systems (Vertellus, 2018). Exposure may occur by inhalation and dermal contact during its production, or when used as an intermediate or as a solvent. Exposure can also occur at coke ovens, oil-shale plants, coffee processing facilities, sewage treatment plants, polymer combustion plants and other similar industries.

In the previous *Monograph* (IARC, 2000), occupational exposure data from the 1970s were summarized for workplaces in the USA where pyridine was manufactured, used as a chemical intermediate, or used as a solvent. Workers were exposed to 8-hour time-weighted average (TWA) pyridine concentrations ranging from 0.026 to 3.240 mg/m^3. A similar range of exposure levels was reported from coke works (0.005–2.980 mg/m^3) in Czechia, with lower levels in blast furnaces, steel works, rolling mills, and foundries (≤ 0.63 mg/m^3) and in a Polish coke by-products plant (≤ 0.7 mg/m^3). However, in a pyridine production area of a coal-tar plant in the Russian Federation, pyridine levels were reportedly 7.5–10 mg/m^3 and occasionally reached 20 mg/m^3 (Izmerov, 1984). According to data from the second half of the 20th century in Poland, pyridine air concentration in various workplaces ranged from 0.002 mg/m^3 to about 20 mg/m^3 (Sapota & Skrzypińska-Gawrysiak, 2013).

Technicians working in quality control and research and development laboratories of a pyridine manufacturer were exposed to low TWA pyridine concentrations (measured over 6-hour periods) of up to 0.29 mg/m^3 (IARC, 2000). Similarly, based on three personal air exposure measurements made in the work environment, an 8-hour TWA pyridine exposure of 0.3 mg/m^3 was estimated for a smell tester who used pyridine as one of their test substances (NIOSH, 1983).

Air samples were collected in the moulding and pouring departments of a United States iron foundry using a phenolic urethane binder. The 2-day average level of pyridine, which was emitted as a breakdown product of 4-phenylpropylpyridine, used as a binder catalyst, was 19 mg/m^3 in the moulding area (NIOSH, 1982). In an investigation near a nylon injection moulding operation at an electrical components plant in the USA, 10 air samples for pyridine were collected. All of these measurements were below the analytical limit of detection, that is, 0.32 mg/m^3 (NIOSH, 1985).

In the United States Occupational Safety and Health Administration (OSHA) database of compliance exposure measurements, 96 measurements of pyridine exposure were collected between 1984 and 2012 from a variety of industries. Seventy percent of the data were below the limit of detection, and more than 90% were less than 0.5 mg/m^3 (OSHA, 2017).

Up to 70 workplace air analyses were performed in the laboratory of the Institut de recherche Robert-Sauvé en santé et en sécurité du travail, Canada, during 1997–2017; only five results were over the limit of detection of their method (0.8 mg/m^3) (IRSST, 2017).

A total of 22 measurements of workplace exposure were collected from the Finnish Institute of Occupational Health during 2012–2016, ranging between 0.0006 and 0.5 mg/m^3. The two highest measurements were recorded at a coffee roasting factory and a waste treatment plant (FIOH, 2017).

1.5 Regulations and guidelines

The Committee of Experts on the Transport of Dangerous Goods and Globally Harmonized System of Classification and Labelling of Chemicals of the United Nations Economic Commission for Europe identified pyridine as United Nations No. 1282, Hazard Class 3, United Nations Packing Group II (UNECE, 2015).

In 2012, the Ministry of the Environment and Climate Change of the province of Ontario, Canada, developed the Ambient Air Quality Criteria (AAQC), which quantifies the desirable

Table 1.2 Eight-hour and short-term limit values for pyridine in different countries or regions

Country or region	8-hour limit value		Short-term limit value	
	ppm	mg/m³	ppm	mg/m³
Australia	5	16		
Austria	5	15	20	60
Belgium	1	3.3		
Canada (Ontario)	1			
Canada (Quebec)	5	16		
China		4		
Denmark	5	15	10	30
Finland	1	3	5[a]	16[a]
France	5	15	10	30
Hungary		15		60
Ireland	5	15	10[b]	30[b]
Latvia	5	15		
Netherlands		0.9		
New Zealand	5	16		
Poland		5		30
Republic of Korea	2	6		
Romania	5	15		
Singapore	5	16		
Spain	1	3		
Sweden	2	7	3[a]	10[a]
Switzerland	5	15	10	30
Turkey	5	15		
United Kingdom	5	16	10	33
United States of America (NIOSH)	5	15		
United States of America (OSHA)	5	15		

NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; ppm, parts per million

[a] 15-minute average value

[b] 15-minute reference period

Source: GESTIS (2017)

concentration of a contaminant in the air based on protection against adverse effects. For pyridine the AAQC are 150 µg/m³ for 24 hours (health) and 80 µg/m³ for 10 minutes (odour) (Ontario Ministry of the Environment and Climate Change, 2012).

In 2004, the European Union (EU) Scientific Committee on Occupational Exposure Limits recommended that occupational exposures to pyridine should be maintained well below 5 ppm (15 mg/m³), but could not derive a health-based limit value, either 8-hour TWA or short-term (15 minutes) exposure limit, from the available data. However, it was noted that because pyridine could be absorbed through the skin, it could pose a threat of systemic toxicity (SCOEL, 2004). Pyridine must not penetrate the sewer system or come into contact with surface water or groundwater (ECHA, 2017).

Pyridine 8-hour limit values (0.9–16.0 mg/m³) and short-term (15 minutes) limit values (10–60 mg/m³) from the GESTIS international limit values database (GESTIS, 2017) are presented in Table 1.2 for different countries.

From 2004, the American Conference of Governmental Industrial Hygienists has recommended a threshold limit value (TLV) 8-hour

TWA of 1 ppm [3.1 mg/m^3] for occupational exposures to pyridine in workplace air. The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits (RELs) of 5 ppm [15 mg/m^3] for pyridine are for up to 10-hour TWAs during a 40-hour working week. The OSHA permissible exposure limit (PEL, 8-hour TWA) for pyridine is 5 ppm (15 mg/m^3) (OSHA, 2018).

Pyridine is listed in the EU Register of Flavouring Substances in accordance with Article 3(1) of EC 2232/96. FL No: 14.008; FEMA No.: 2966; CoE No.: 604; Chemical Group 28 (Vertellus, 2018). Thirty-two pyridine derivatives are included in the list of approved flavouring substances of Commission Implementing Regulation (EU) No. 872/2012 (EU, 2012).

The European Medicines Agency classified pyridine as a class 2 solvent in new veterinary medicinal products with a permitted daily exposure (PDE) of 2.0 mg/day and a concentration limit of 200 ppm (EMA, 2000). The United States Department of Health and Human Services Food and Drug Administration also issued a guidance for the industry on pharmaceuticals for human use with a similar classification, PDE, and concentration limit (FDA, 2012).

2. Cancer in Humans

A cohort study of mortality of 729 men manufacturing 4,4′-bipyridyl [4,4′-bipyridine] in England (Paddle et al., 1991) was reviewed in the previous evaluation of pyridine by the Working Group in 2000 (IARC, 2000) (pyridine is used in the manufacture of 4,4′-bipyridyl, which is used to make paraquat). Standardized mortality ratios (SMRs) for cancer outcomes were reported only for all cancers combined and for cancer of the lung. For all cancers combined, the standardized mortality ratio was 1.1 (95% confidence interval (CI), 0.7–1.5; 29 deaths) and for cancer of the lung it was 1.2 (95% CI, 0.7–2.1; 13 deaths). The cancer of the lung risks were investigated in a nested case–referent study and various subcohort analyses, but no quantitative results of these analyses or data on the relationship between cancer of the lung and exposure to pyridine were reported.

An earlier case-series study of skin lesions in the same plant had identified 99 chemicals used in the 4,4′-bipyridyl manufacturing process (Bowra et al., 1982). A total of 6 cases of Bowen's disease and 6 cases of squamous cell carcinoma were observed, but no cancer risk data were reported.

[No quantitative exposure data were available from these studies, and associations between cancer risk and exposure to pyridine were not reported.]

3. Cancer in Experimental Animals

Pyridine was evaluated by the Working Group in 2000 (IARC, 2000), which concluded that there was *limited evidence* for the carcinogenicity of pyridine in experimental animals.

Studies of the carcinogenicity of pyridine, given in drinking-water, in mice and rats have been conducted (NTP, 2000), the results of which are summarized in Table 3.1.

3.1 Mouse

3.1.1 Oral administration

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 7 weeks) were given pyridine (purity, > 99%) in drinking-water at doses of 0 (control), 125 (females only), 250, 500, or 1000 (males only) ppm, equivalent to average daily doses of 0, 35, 65, or 110 mg/kg body weight (bw) in males and 0, 15, 35, or 70 mg/kg bw in females, for 104 weeks (males) or 105 weeks (females) (NTP, 2000).

The survival of exposed males and females was similar to that of controls. Final mean body weights of females given pyridine at doses of

Table 3.1 Studies of carcinogenicity with pyridine in rodents

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 7 wk 104 wk NTP (2000)	Drinking-water Pyridine, > 99% Deionized water 0, 250, 500, 1000 ppm (0, 35, 65, 110 mg/kg bw/d) continuously 50, 50, 50, 50 35, 28, 34, 35	*Liver* Hepatocellular adenoma (multiple): 16/50*, 29/50**, 29/49**, 28/50**	*[$P = 0.018$ (trend), Cochran-Armitage test] **$P \leq 0.05$	Principal strengths: GLP study in both males and females Statistical test, poly-3 test if not otherwise specified
		Hepatocellular adenoma (includes multiple): 29/50*, 40/50**, 34/49, 39/50***	*$P = 0.031$ (trend) **$P = 0.003$ ***$P = 0.011$	
		Hepatocellular carcinoma (multiple): 3/50*, 19/50**, 26/49**, 18/50**	*[$P < 0.001$ (trend), Cochran-Armitage test] **$P \leq 0.01$	
		Hepatocellular carcinoma (includes multiple): 15/50*, 35/50**, 41/49**, 40/50**	*$P < 0.001$ (trend) **$P < 0.001$	
		Hepatoblastoma (multiple): 1/50, 4/50, 6/49*, 2/50	*$P \leq 0.05$	
		Hepatoblastoma (includes multiple): 2/50*, 18/50**, 22/49**, 15/50**	*$P = 0.005$ (trend) **$P < 0.001$	
		Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined): 38/50*, 47/50**, 46/49***, 47/50****	*$P < 0.001$ (trend) **$P = 0.002$ ***$P = 0.003$ ****$P < 0.001$	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (F) 7 wk 105 wk NTP (2000)	Drinking-water Pyridine, > 99% Deionized water 0, 125, 250, 500 ppm (0, 15, 35, 70 mg/kg bw/d) continuously 50, 50, 50, 50 32, 30, 22, 29	*Liver* Hepatocellular adenoma (multiple): 24/49, 34/50*, 37/50**, 30/50 Hepatocellular adenoma (includes multiple): 37/49, 39/50, 43/50*, 34/50 Hepatocellular carcinoma (multiple): 3/49*, 11/50**, 14/50***, 30/50*** Hepatocellular carcinoma (includes multiple): 13/49*, 23/50**, 33/50***, 41/50*** Hepatoblastoma (multiple): 0/49, 0/50, 3/50, 4/50 Hepatoblastoma (includes multiple): 1/49*, 2/50, 9/50**, 16/50*** Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined): 41/49*, 42/50, 45/50**, 44/50***	 *$P \leq 0.05$ **$P \leq 0.01$ *$P = 0.015$ *[$P < 0.001$ (trend), Cochran-Armitage test] **$P \leq 0.05$ ***$P \leq 0.01$ *$P < 0.001$ (trend) **$P = 0.014$ ***$P < 0.001$ NS *$P < 0.001$ (trend) **$P = 0.007$ ***$P < 0.001$ *$P = 0.009$ (trend) **$P = 0.042$ ***$P = 0.045$	Principal strengths: GLP study in both males and females Statistical test, poly-3 test if not otherwise specified

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 7 wk 104 wk NTP (2000)	Drinking-water Pyridine, > 99% Deionized water 0, 100, 200, 400 ppm (0, 7, 14, 33 mg/kg bw/d) continuously 50, 50, 50, 50 25, 20, 25, 16	*Kidney* Renal tubule adenoma, standard evaluation (single section) 1/50*, 0/48, 2/50, 6/49** Renal tubule carcinoma, standard evaluation (single section) 0/50, 1/48, 0/50, 0/49 Renal tubule adenoma or carcinoma (combined), standard evaluation (single section) 1/50*, 1/48, 2/50, 6/49** Renal tubule adenoma, extended evaluation (step sections) 1/50*, 3/48, 5/50, 9/49** Renal tubule adenoma, standard (single section) and extended (step sections) evaluations combined 2/50*, 3/48, 6/50, 10/49** Renal tubule carcinoma, standard (single section) and extended (step sections) evaluations combined 0/50, 1/48, 0/50, 0/49 Renal tubule adenoma or carcinoma (combined), standard (single section) and extended (step sections) evaluations combined 2/50*, 4/48, 6/50, 10/49**	 *P = 0.003 (trend) **P = 0.042 NS *P = 0.008 (trend) **P = 0.042 *[P = 0.031 (trend), Cochran-Armitage test] **$P \leq 0.01$ *P = 0.002 (trend) **P = 0.008 NS *P = 0.003 (trend) **P = 0.008	Principal strengths: GLP study in both males and females Statistical test, poly-3 test if not otherwise specified; historical incidence: renal tubule adenoma, 1/327 and renal tubule carcinoma, 0/327

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N (F) 7 wk 105 wk NTP (2000)	Drinking-water Pyridine, > 99% Deionized water 0, 100, 200, 400 ppm (0, 7, 14, 33 mg/kg bw/d) continuously 50, 50, 50, 50 32, 37, 29, 26	*All organs*, mononuclear cell leukaemia: 12/50*, 16/50, 22/50**, 23/50***	*P = 0.013 (trend) **P = 0.043 ***P = 0.020	Principal strengths: GLP study in both males and females Statistical test, poly-3 test
Full carcinogenicity Rat, Wistar (M) 7 wk 104 wk NTP (2000)	Drinking-water Pyridine, > 99% Deionized water 0, 100, 200, 400 ppm (0, 8, 17, 36 mg/kg bw/d) continuously 50, 50, 50, 50 22, 14, 11, 7	*Testis*, testicular (interstitial cell) adenoma: 5/50*, 6/49, 4/49, 12/50**	*P = 0.008 (trend) **P = 0.012	Principal strengths: GLP study Statistical test, poly-3 test

bw, body weight; d, day(s); F, female; GLP, good laboratory practice; M, male; NS, not significant; wk, week(s)

250 ppm and 500 ppm were 73% and 70% that of controls, respectively. Final mean body weights of all groups of treated male mice and the group of female mice given pyridine at 125 ppm were within 10% of that of controls. Water consumption by males exposed to pyridine at 250 or 500 ppm was generally greater than that by controls during the second year of the study; male mice exposed to pyridine at 1000 ppm consumed less water than controls throughout the entire study. Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year of the study. [The Working Group noted that water consumption in exposed females was at least 30% greater than that of controls during the second year of the study; the authors did not suggest that this had any influence on study results.]

Treated male and female mice had significant increases in the incidences (generally with a significant positive trend) of hepatocellular neoplasms and hepatoblastoma [an embryonal tumour of the liver cells]. Compared with controls, in male mice given pyridine at 250, 500, and 1000 ppm, these included increases in the incidence of: hepatocellular adenoma (multiple): 16/50 (control), 29/50 ($P \leq 0.05$), 29/49 ($P \leq 0.05$), and 28/50 ($P \leq 0.05$); hepatocellular adenoma (includes multiple): 29/50 (control), 40/50 ($P = 0.003$), 34/49, and 39/50 ($P = 0.011$); hepatocellular carcinoma (multiple): 3/50 (control), 19/50 ($P \leq 0.01$), 26/49 ($P \leq 0.01$), and 18/50 ($P \leq 0.01$); hepatocellular carcinoma (includes multiple): 15/50 (control), 35/50 ($P < 0.001$), 41/49 ($P < 0.001$), and 40/50 ($P < 0.001$); hepatoblastoma (multiple): 1/50 (control), 4/50, 6/49 ($P \leq 0.05$), and 2/50; and hepatoblastoma (includes multiple): 2/50 (control), 18/50 ($P < 0.001$), 22/49 ($P < 0.001$), and 15/50 ($P < 0.001$). The incidences for the combination of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma were: 38/50 (control), 47/50 ($P = 0.002$), 46/49 ($P = 0.003$), and 47/50 ($P < 0.001$).

Compared with controls, in female mice given pyridine at 125, 250, and 500 ppm there were increases in the incidences (generally with a significant positive trend) of: hepatocellular adenoma (multiple): 24/49 (control), 34/50 ($P \leq 0.05$), 37/50 ($P \leq 0.01$), and 30/50; hepatocellular adenoma (includes multiple): 37/49 (control), 39/50, 43/50 ($P = 0.015$), and 34/50; hepatocellular carcinoma (multiple): 3/49 (control), 11/50 ($P \leq 0.05$), 14/50 ($P \leq 0.01$), and 30/50 ($P \leq 0.01$); hepatocellular carcinoma (includes multiple): 13/49 (control), 23/50 ($P = 0.014$), 33/50 ($P < 0.001$), and 41/50 ($P < 0.001$); hepatoblastoma (multiple): 0/49 (control), 0/50, 3/50, and 4/50; and hepatoblastoma (includes multiple): 1/49 (control), 2/50, 9/50 ($P = 0.007$), and 16/50 ($P < 0.001$). The incidences for the combination of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma were: 41/49 (control), 42/50, 45/50 ($P = 0.042$), and 44/50 ($P = 0.045$) (NTP, 2000). [The Working Group noted this was a well-conducted good laboratory practice (GLP) study and the use of both sexes.]

3.1.2 *Transgenic models*

Transgenic mouse models were developed to characterize carcinogens, including a $p53^{+/-}$ mouse model that responds to genotoxic chemicals, and a Tg.Ac model that was reported to respond to genotoxic and non-genotoxic carcinogens (Tennant et al., 1996). Pyridine was tested in both of these models for evidence of treatment-related lesions (Spalding et al., 2000). In the Tg.Ac model, pyridine was administered to hemizygous females (age, 14 weeks) by skin application at doses of 0, 1.5, 3.0, or 6.0 mg for 20 weeks. Pyridine was added to the feed of the $p53^{+/-}$ mice (age, 8–11 weeks) at doses of 0, 250, 500, or 1000 ppm (males) and 0, 125, 250, or 500 ppm (females) for 26 weeks. Gross necropsy was performed on all animals in both transgenic models at 26 weeks. Tissues from multiple organs of control mice and mice given the highest dose

were examined microscopically. In addition, in the Tg.Ac model, a section of the skin at the site of application was examined microscopically. Tg.Ac mice treated three times a week with 1.25 μg 12-*O*-tetradecanoylphorbol-13-acetate (used as a positive control) had a 100% incidence of skin papillomas. No significant increase in the incidence of neoplasms was observed in either of the transgenic mouse models exposed to pyridine (Spalding et al., 2000). [The Working Group noted the difficulty in evaluating these short-term gene-specific transgenic assays because they may not provide critical information that can be obtained from longer-term bioassays (e.g. effects on multiple target organs, effects with time and age) (Pritchard et al., 2003).]

3.2 Rat

3.2.1 Oral administration

Groups of 50 male and 50 female F344/N rats (age, 7 weeks) were given pyridine (purity, > 99%) in drinking-water at doses of 0 (control), 100, 200, or 400 ppm, equivalent to average daily doses of 0, 7, 14, or 33 mg/kg bw for 104 weeks (males) or 105 weeks (females) (NTP, 2000).

The survival of exposed males and females was similar to that of controls. Final mean body weights of male and female rats given pyridine at 200 ppm were 81% and 89% of those of male and female controls, respectively. Final mean body weights of male and female rats given pyridine at 400 ppm were 80% and 84% those of male and female controls, respectively. The final mean body weights of both male and female rats given pyridine at 100 ppm were within 5% of the final mean body weight of controls. Water consumption by male and female rats given pyridine at 400 ppm was greater than that of controls throughout the study, and water consumption by males and females given pyridine at 200 ppm was greater during the second year of the study.

Incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in male rats exposed to pyridine at 400 ppm were significantly increased (with a significant positive trend) compared with controls. Compared with controls, in the standard kidney evaluation (single section) of male rats given pyridine at 100, 200, and 400 ppm there were observed incidences of: renal tubule adenoma: 1/50 (2%, control), 0/48, 2/50 (4%), and 6/49 (12%, $P = 0.042$); renal tubule carcinoma: 0/50 (control), 1/48 (2%), 0/50, and 0/49; and renal tubule adenoma or carcinoma (combined): 1/50 (2%, control), 1/48 (2%), 2/50 (4%), and 6/49 (12%, $P = 0.042$). The incidences of renal tubule neoplasms in all groups of exposed male rats equalled or exceeded the historical control ranges (single section) for drinking-water studies of 1/327 (renal tubule adenoma only) (0.3% ± 0.8%), range 0–2%. In this standard kidney evaluation, increased incidence of renal tubule hyperplasia was observed in the groups of males given pyridine at 200 ppm (4/50, 8%) and 400 ppm (7/49, 14%, $P \leq 0.05$) compared with controls (1/50, 2%) and those given pyridine at 100 ppm (0/48). In the extended evaluation of the kidney (step sections), the incidences of renal tubule adenoma were 1/50 (2%, control), 3/48 (6%), 5/50 (10%), and 9/49 (18%, $P \leq 0.01$) for male rats given pyridine at 0, 100, 200, and 400 ppm, respectively. There were no additional rats with carcinomas found in the extended evaluation.

In the original (single section) and extended (step sections) evaluations (combined) of the kidney of male rats, there were observed incidences of: renal tubule adenoma: 2/50 (4%, control), 3/48 (6%), 6/50 (12%), and 10/49 (20%, $P = 0.008$); renal tubule carcinoma: 0/50 (control), 1/48 (2%), 0/50, and 0/49; and renal tubule adenoma or carcinoma (combined): 2/50 (4%, control), 4/48 (8%), 6/50 (12%), and 10/49 (20%, $P = 0.008$).

The incidences of mononuclear cell leukaemia in female rats were significantly increased with a significant positive trend in the 200 and 400 ppm

groups: 12/50 (24%, control), 16/50 (32%), 22/50 (44%, $P = 0.043$), and 23/50 (46%, $P = 0.020$). The incidence in the group given pyridine at 400 ppm exceeded the historical control range. In female rats, the historical incidence of mononuclear cell leukaemia for drinking-water studies was 102/330 (30.9 ± 10.0%), range 16–44% (NTP, 2000). [The Working Group noted that mononuclear cell leukaemia can occur spontaneously in female rats. The strengths of this study were its well-conducted GLP design and the use of both sexes.]

Groups of 50 male Wistar rats (age, 7 weeks) were given pyridine (purity, > 99%) in drinking-water at doses of 0 (control), 100, 200, or 400 ppm, equivalent to average doses of 0, 8, 17, or 36 mg/kg bw per day, for 104 weeks (NTP, 2000). Pyridine was shown to increase the incidence of leukaemia in a transplant model for leukaemia in male F344/N rats (Dieter et al., 1989), and male Wistar rats were used to evaluate the effects of pyridine in a rat model with a low spontaneous incidence of mononuclear cell leukaemia.

The survival of exposed rats given pyridine at 200 or 400 ppm was significantly less than that of controls; the numbers of rats surviving at the end of the study were 22/50 (control), 14/50, 11/50 ($P = 0.020$), and 7/50 ($P < 0.001$). Final mean body weights of rats exposed to 200 ppm or 400 ppm were significantly less than that of controls at 83% and 84%, respectively. Water consumption by control and exposed rats was similar.

There was a significant increase in the incidence of testicular (interstitial cell) adenoma in rats exposed to 400 ppm, with observed incidences of 5/50 (10%, control), 6/49 (12%), 4/49 (8%), and 12/50 (24%, $P = 0.012$) with a significant positive trend. [There were no historical control data for this tumour for male Wistar rats.] The incidences of interstitial cell hyperplasia observed in exposed groups were numerically greater than those in controls, but these increases – 3/50 (6%, control), 4/49 (8%), 7/49 (14%), and 7/50 (14%) – were not significant.

[The Working Group noted that in this male Wistar rat model there were no statistical increases in the incidence of mononuclear cell leukaemia that were related to treatment. The Working Group also noted that the male Wistar rat kidney was evaluated in a manner similar to that for the male F344/N rat, but the incidences of renal cell tumours in exposed male Wistar rats compared with control rats were not significantly increased.]

There were treatment-related liver non-neoplastic lesions in exposed male Wistar rats, including centrilobular degeneration and necrosis, fibrosis, and pigmentation (NTP, 2000). [The Working Group noted this was a well-conducted GLP study.]

3.2.2 Subcutaneous injection

Groups of male and female Fischer 344 rats (age, ~6 weeks) were injected subcutaneously with pyridine [commercial product] in saline at 0, 3, 10, 30, or 100 mg/kg bw twice a week for 52 weeks. The animals were then kept in observation for an additional 6 months. The number of animals in each group varied with the dose level: there were 60 rats per sex (negative control, no treatment), 60 rats per sex at 0 mg/kg bw (saline control), 10 rats per sex at 3 mg/kg bw, 20 rats per sex at 10 mg/kg bw, 30 rats per sex at 30 mg/kg bw, and 40 rats per sex at 100 mg/kg bw. There was no treatment-related effect on survival, and the final mean body weights of the male and female rats given pyridine at 100 mg/kg bw were 1–6% less than those of the negative or saline controls. All spontaneous deaths, moribund rats, and rats showing gross microscopic changes were examined histologically. Selected histopathological results were reported with findings from all dose levels combined. There was no significant increase in tumour incidence (Mason et al., 1971).

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Absorption, distribution, and excretion

(a) Humans

As noted in previous reports (ATSDR, 1992; European Commission, 2004), human data for pyridine are sparse and no data are available from exposure by inhalation. Pyridine at a dose of 3.4 mg of [^{14}C]-labelled pyridine (~0.04 mg/kg bw) was administered orally in orange juice to two healthy male subjects and 24-hour urine samples were collected (D'Souza et al., 1980; Damani et al., 1982). Only 65% and 68% of the dose was recovered in the two volunteers, about half of which was recovered as pyridine *N*-oxide and about 10% and 20% of which was recovered as *N*-methylpyridinium ion.

(b) Experimental systems

No studies of exposure by inhalation were available to the Working Group. However, the absorption, distribution, and excretion of pyridine have been described after either oral exposure or intraperitoneal injection in multiple experimental animal species, including rats, mice, rabbits, gerbils, and hamsters. As in humans, pyridine is absorbed by various tissues in a dose-dependent manner, but there is no tissue accumulation due to rapid elimination in urine, faeces, and exhaled breath (ATSDR, 1992).

Significant species- and dose-dependent differences have been reported. For example, urinary excretion of pyridine *N*-oxide after mice, hamsters, rats, guinea-pigs, rabbits, and ferrets were given pyridine by intraperitoneal injection varied from 10% of the dose in rats to almost 40% in mice and guinea-pigs (Gorrod & Damani, 1980). A comparison of urinary excretion in several species (i.e. rats, guinea-pigs, mice, gerbils, hamsters, rabbits, and cats) given intraperitoneal injections of [^{14}C]-labelled pyridine (7 mg/kg bw) showed marked species differences in the extent of recovery, ranging from 48% of the total dose in rats to 75% in cats (D'Souza et al., 1980). In the same study, comparisons of urinary excretion after either oral or intraperitoneal administration revealed similar rates of recovery for a given species regardless of route of administration. This observation is consistent with the rapid and virtually complete absorption of pyridine regardless of route of administration.

4.1.2 Metabolism

(a) Humans

As shown in Fig. 4.1, the initial metabolic reaction is catalysed primarily by cytochrome P450 (CYP) 2E1. In the human study described above (Section 4.1.1a), formation of pyridine *N*-oxide was the predominant route of metabolism. An in vitro study in microsomes from human liver, kidney, and lung (Wilke et al., 1989) showed tissue-specific patterns of metabolism. Pyridine *N*-oxide was the predominant metabolite produced from liver microsomes, the second most abundant from kidney microsomes, and the equally abundant metabolite from lung microsomes. Evidence for formation of 2,5-dihydroxypyridine, discussed below in Section 4.1.2(b), is only available from studies in experimental systems.

(b) Experimental systems

As shown in Fig. 4.1, pyridine metabolism yields a diversity of potential metabolites. Pyridine *N*-oxide is generally the predominant metabolite recovered in urine in all species studied. However, the distribution of metabolites varies markedly across species and tissues. The metabolite *N*-methylated pyridinium ion is particularly variable among species and according to pyridine dose. Damani et al. (1982)

showed that *N*-methylation is the preferred initial metabolic step at low doses, whereas *N*-oxidation can account for up to 10% in rats to as much as 20–40% in other species, including rabbits, mice, hamsters, guinea-pigs, and ferrets, at higher doses.

Oxidative pyridine metabolism is initiated by CYPs, as evidenced by generation of metabolites in preparations of tissue (primarily liver) microsomes that require a reduced nicotinamide adenine dinucleotide phosphate generating system, and produces spectral shifts characteristic of substrate binding to heme moieties on CYPs (Hlavica et al., 1982). CYP2E1 is the primary enzyme that catalyses the primary reaction, *N*-oxide formation; other CYPs only seem to play a quantitatively significant role at high pyridine concentrations (Kim et al., 1991a). Competitive inhibition of pyridine *N*-oxidation by the presence of *para*-nitrophenol is also indicative of the major role of CYP2E1.

One metabolite of potential toxicological importance because of its chemical reactivity is 2,5-dihydroxypyridine, which can undergo redox cycling, generating reactive oxygen species. Rabbit liver microsomes metabolized both the 3-hydroxy and 2-hydroxy metabolites of pyridine to 2,5-dihydroxy metabolite (Kim & Novak, 1990a). Three CYPs catalyse the reaction, with markedly different relative contributions and rates by substrate. The rate of CYP2E1 catalysis was 15- to 30-fold greater than that of either CYP2B1 or CYP1A2 catalysis with 3-hydroxypyridine as substrate. With 2-hydroxypyridine as substrate, the rate of CYP2E1 activity was 10-fold that of CYP1A2, with no detectable activity by CYP2B1.

4.1.3 Modulation of metabolic enzymes

(a) Humans

Pyridine or some of its metabolites can alternately induce or inhibit expression of CYP1A1/1A2 and/or CYP2E1. *CYP1A1* mRNA transcripts were detected in all human lung samples from 27 subjects, and were induced by both pyridine (12.4 mM) or 2-hydroxypyridine (10 mM) (Wei et al., 2002). In contrast, *CYP1A2* mRNA was variably detected and was only inducible in some of the tissue samples. In HepG2 cells, only 2-hydroxypyridine (among four metabolites tested, and the parent compound) induced *CYP1A1* mRNA expression and increased ethoxyresorufin-*O*-deethylase activity (Iba et al., 2002). Pyridine only induced *CYP1A1* expression when cells were first engineered to express human CYP2E1, indicating that a pyridine metabolite is responsible for the induction.

(b) Experimental systems

(i) CYP2E1 induction

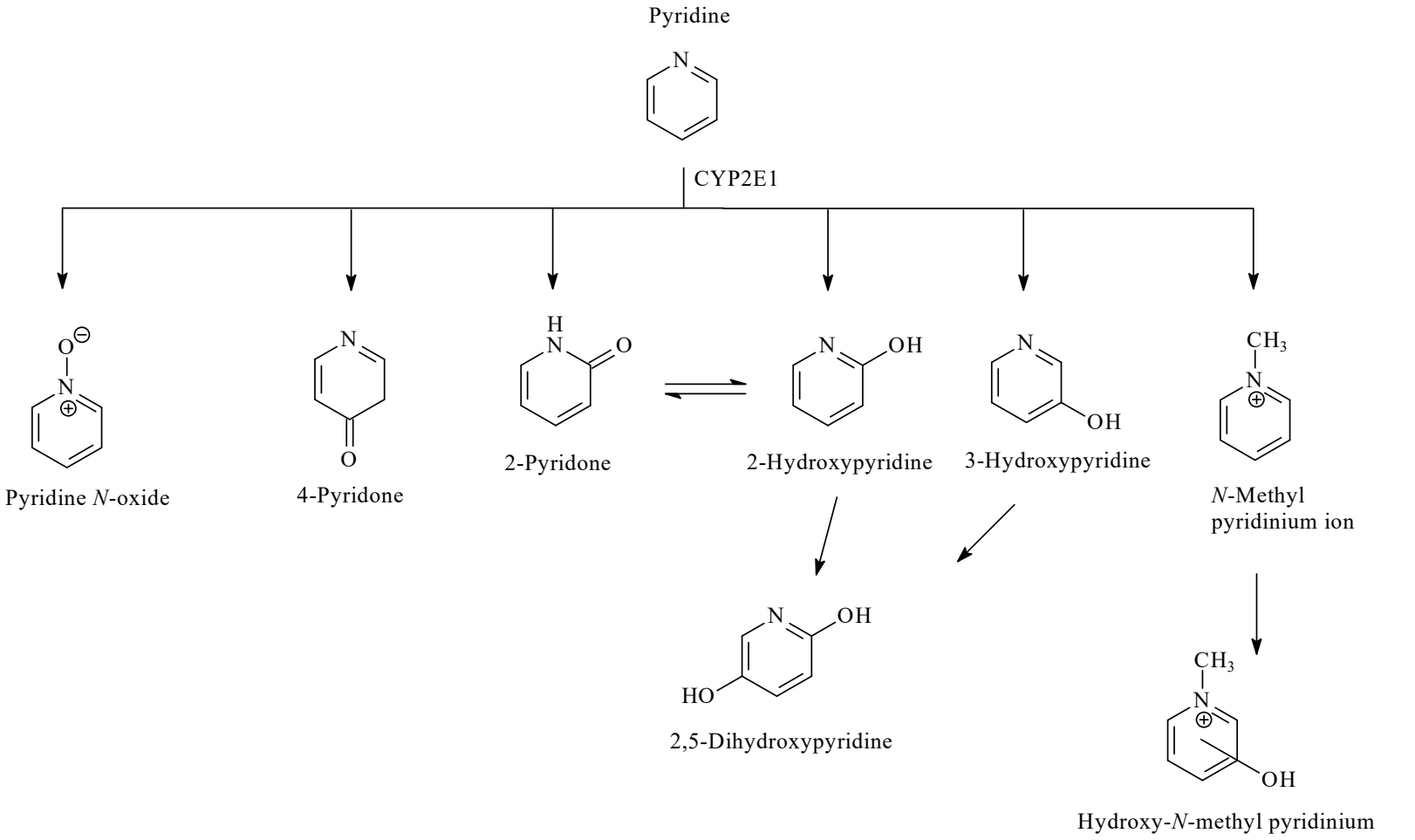
Considerable data are available on the use of pyridine as an inducing agent for CYPs. While CYP2E1 is the primary focus of most studies, other CYPs, including CYP2B1 and CYP1A1/1A2, are also induced in certain tissues and certain species.

Induction of rat liver CYP2E1 has been extensively studied, primarily by intraperitoneal injection of pyridine (e.g. Carlson & Day, 1992; Kim et al., 1993; Cummings et al., 2001; González-Jasso et al., 2003). Hotchkiss et al. (1993) studied pyridine inhalation in rats, reporting significant hepatic induction of CYP2E1 at concentrations equivalent to the threshold limit value of 5 ppm.

Pyridine induction of CYP2E1 has been characterized in other rodent tissues, including rat kidney (Kim et al., 1992; Hotchkiss et al., 1995; Cummings et al., 2001), rat lung (Carlson & Day, 1992; Page & Carlson, 1994), rat prostate and testis (Jiang et al., 1998), rat peripheral lymphocytes (González-Jasso et al., 2003), and mouse liver and lung (Page & Carlson, 1994).

Pyridine increases CYP2E1 protein levels and enzymatic activity, but not mRNA levels (e.g. Kim & Novak, 1990a). The mechanism involves increased translational efficiency with no effect

Fig. 4.1 Metabolic pathways for pyridine



The scheme illustrates the identified metabolites of pyridine, most of which derive from the initial catalysis by cytochrome P450 2E1 (CYP2E1). The rate of formation of each metabolite of pyridine differs among tissues and species. Whereas most of the metabolites have been identified in all species studied, 2,5-dihydroxypyridine has only been characterized in rabbit liver microsomes. 2-Pyridone and 2-hydroxypyridine are in rapid equilibrium with each other.
Compiled by the Working Group.

on transcription. As examples of its impact on the metabolism of other chemicals, the intraperitoneal administration of pyridine increased carbon tetrachloride metabolism in rat liver (Gruebele et al., 1996), styrene metabolism and styrene-induced pneumo- and hepatotoxicity in mice (Gadberry et al., 1996; Carlson, 1997), and CYP2E1-catalysed reductive dehalogenation and subsequent hepatotoxicity of 1,1-dichloro-1-fluoroethane (HCFC-141b) (Zanovello et al., 2001). In contrast, pyridine administration had no effect on pulmonary or hepatic cell injury in rats due to acrylonitrile (Felten et al., 1998), on benzene-induced clastogenicity in mice (Harper et al., 1984), or on benzene-induced pneumotoxicity and hepatotoxicity in rats (Chaney & Carlson, 1995).

(ii) Other CYPs

Iba et al. (1999a) showed that pyridine produced complex and tissue-, sex-, and enzyme-specific effects on CYP1A enzymes in Sprague-Dawley rats. Pyridine treatment of rats induced activities of CYP1A1 and CYP1A2, but the response varied according to sex and tissue, and was generally greater for CYP1A1 (Kim et al., 1991b; Kim et al., 1995). Fung et al. (1999) observed induction of CYP1A1, but not CYP1A2, in rat peripheral blood lymphocytes that was associated with an increase in the in vivo bioactivation and bacterial mutagenicity of benzo[*a*]pyrene.

CYP2B enzymes in experimental animal tissues are also induced by pyridine, but the underlying mechanism, kinetics, and tissue specificity differ from that by which induction of CYP2E1 occurs (Park et al., 1992; Kim et al., 1993).

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

See Table 4.1, Table 4.2, and Table 4.3.

The genotoxicity data for pyridine were reviewed by the NTP (2000) and IARC (2000). A summary of those data and of one report published since then, describing a study in *Drosophila melanogaster* (Muñoz & Barnett, 2003), is provided in the following section.

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Mammalian systems

In a study in vivo, pyridine did not induce micronuclei in orally exposed male ICR mice (Harper et al., 1984) and did not induce micronuclei or chromosomal aberrations in intraperitoneally injected male B6C3F$_1$ mice (NTP, 2000). In male B6C3F$_1$ mice given pyridine by oral gavage (175, 350, and 700 mg/kg bw), no indication of unscheduled DNA synthesis was detected in hepatocytes harvested 2 and 16 hours after dosing (MacGregor et al., 2000).

In a study in vitro, no significant increases in mutant frequencies were seen in L5178Y *Tk*$^{+/-}$ mouse lymphoma cell cultures after incubation with pyridine (≤ 5000 µg/mL), with or without rat liver S9 (McGregor et al., 1988). Pyridine was also negative for induction of chromosomal aberrations in Chinese hamster cells in the absence or presence of S9 (Abe & Sasaki, 1977; Ishidate & Odashima, 1977; NTP, 2000). Sister-chromatid exchanges were increased in one study in Chinese hamster cells (without exogenous metabolic activation) (Abe & Sasaki, 1977), but not in another study of Chinese hamster ovary cells with or without S9 (NTP, 2000).

(ii) Non-mammalian systems

Pyridine yielded mixed results in experiments for induction of sex-linked recessive lethal (SLRL) mutations in adult male *D. melanogaster* (Valencia et al., 1985; Mason et al., 1992; Foureman et al., 1994). Valencia et al. (1985) reported negative results for pyridine administered by intraperitoneal injection (at 7000 ppm in aqueous 0.7% saline solution),

Table 4.1 Genetic and related effects of pyridine in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Micronuclei	Mouse, ICR (M)	Bone marrow (PCE)	–	1000 mg/kg bw	Gavage, 1×	1000 PCEs scored per each of 5 mice per dose group	Harper et al. (1984)
Unscheduled DNA synthesis	Mouse, B6C3F$_1$ (M)	Liver	–	700 mg/kg bw	Gavage, 1×		MacGregor et al. (2000)
Chromosomal aberrations	Mouse, B6C3F$_1$ (M)	Bone marrow	–	600 mg/kg bw	i.p., 1×; sampling at 17 and 36 h		NTP (2000)
Micronuclei	Mouse, B6C3F$_1$ (M)	Bone marrow	–	500 mg/kg bw	i.p., 3× at 24 h intervals; sampling 24 h after final injection		NTP (2000)

bw, body weight; h, hour(s); HID, highest ineffective dose; i.p., intraperitoneal; LED, lowest effective dose; M, male; PCE, polychromatic erythrocyte

[a] –, negative

Table 4.2 Genetic and related effects of pyridine in non-human mammalian cells in vitro

End-point	Species, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Chromosomal aberrations	Chinese hamster, Don cells	–	NT	5 mM [396 µg/mL]		Abe & Sasaki (1977)
Sister-chromatid exchange	Chinese hamster, Don cells	+	NT	1 mM [79.10 µg/mL]		Abe & Sasaki (1977)
Chromosomal aberrations	Chinese hamster, lung	–	NT	505.7 mg/mL		Ishidate & Odashima (1977)
Mutation	Mouse, L5178 *Tk*$^{+/-}$, lymphoma cells	–	–	5000 µg/mL	Little cytotoxicity at the HIC (relative total growth, 62–77%)	McGregor et al. (1988)
Chromosomal aberrations	Chinese hamster, ovary	–	–	5000 µg/mL		NTP (2000)
Sister-chromatid exchange	Chinese hamster, ovary	–	–	5020 µg/mL	HIC without S9, 1673 µg/mL	NTP (2000)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested; S9, 9000 × *g* supernatant from rat liver; *Tk*$^{+/-}$, thymidine kinase locus

[a] +, positive; –, negative

Table 4.3 Genetic and related effects of pyridine and its metabolites in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]		Agent, concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Pyridine						
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	–	–	Pyridine, 3 µmol/plate [237 µg/plate]		Florin et al. (1980)
Salmonella typhimurium TA98 and TA100, TA1535, TA1537	Reverse mutation	–	–	Pyridine, 10 000 µg/plate		Haworth et al. (1983)
Drosophila melanogaster	Sex-linked recessive lethal mutations	+/–	NA	Pyridine, 700 ppm	Equivocal results by feeding ($P = 0.043$); negative results by injection (HIC, 7000 ppm)	Valencia et al. (1985)
Saccharomyces cerevisiae D61.M	Aneuploidy	+	NT	Pyridine, 0.99%		Zimmermann et al. (1986)
ϕX-174 RF double-stranded plasmid DNA	DNA strand breaks	–	NT	Pyridine, 1 mM [79 µg/mL]	Only a single dose tested	Kim & Novak (1990b)
Drosophila melanogaster	Sex-linked recessive lethal mutations	+	NA	Pyridine, 4300 ppm	Injection; negative results by feeding (500 ppm)	Mason et al. (1992)
Drosophila melanogaster	Sex-linked recessive lethal mutations	–	NA	Pyridine, 500 ppm	Negative results by injection (500 ppm) or by feeding (730 ppm)	Foureman et al. (1994)
Drosophila melanogaster	Aneuploidy	+	NA	Pyridine, 0.05%		Muñoz & Barnett (2003)
Pyridine metabolites						
Escherichia coli W3110 and AB1157 and DNA repair-deficient derivatives; *Bacillus subtilis* wild-type and UV-sensitive mutants	Other	–	NT	Pyridine 1-oxide [pyridine *N*-oxide], 500 µg		Nagao & Sugimura (1972)
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	–	–	3-Hydroxypyridine [3-pyridinol], 3 µmol/plate [285 µg/plate]		Florin et al. (1980)
Salmonella typhimurium TA98, TA100; *Klebsiella pneumoniae*, *E. coli*	Mutation	–	NT	Pyridine 1-oxide [pyridine *N*-oxide], 100 mM [9510 µg/mL]		Voogd et al. (1980)

Table 4.3 (continued)

Test system (species, strain)	End-point	Results[a]		Agent, concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
ϕX-174 RF double-stranded plasmid DNA	DNA strand breaks	+	NT	2.5-Dihydroxypyridine EC_{50}, 60 µM [6.7 µg/mL]	Catalase (0.5–1.0 µg) inhibited formation of DNA strand breaks	Kim & Novak (1990b)
ϕX-174 RF double-stranded plasmid DNA	DNA strand breaks	–	NT	3-Hydroxypyridine, 1 mM [95 µg/mL]	Only a single dose tested	Kim & Novak (1990b)

EC_{50}, half maximal effective concentration; HIC, highest ineffective concentration; LEC, lowest effective concentration; NA, not applicable; NT, not tested; ppm, parts per million; RF, replicative form; UV, ultraviolet radiation

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study)

whereas feeding (at 700 ppm pyridine in aqueous 5% sucrose) modestly increased recessive lethal mutations (P = 0.043). A second experiment using both intraperitoneal injection (at 500 ppm) and feeding (at 730 ppm) routes yielded negative results (Foureman et al., 1994). In a third study (Mason et al., 1992), results of a feeding (at 500 ppm) experiment were negative, but administration of pyridine by intraperitoneal injection (at 4300 ppm) significantly increased the frequency of SLRL mutations. A follow-up test for induction of reciprocal translocations in germ cells of male *D. melanogaster* given pyridine produced negative results (Mason et al., 1992). Finally, increased frequencies of nondisjunction were observed in *D. melanogaster* broods arising from nearly mature oocytes, but not early-stage or mature oocytes, after females were fed pyridine (at 0.05, 0.1, 0.2, and 0.3%) and mated to untreated males (Muñoz & Barnett, 2003).

Zimmermann et al. (1986) reported induction of aneuploidy, likely from disruption of microtubule assembly, in *Saccharomyces cerevisiae* D61.M after treatment with up to 1.09% pyridine. Pyridine was negative in bacterial reverse mutation assays in various *Salmonella typhimurium* strains tested with and without S9 mix (Florin et al., 1980; Haworth et al., 1983).

Pyridine (1 mM, single dose) did not induce DNA strand breaks in ϕX-174 phage DNA (Kim & Novak, 1990b).

(iii) Metabolites of pyridine

Few mutagenicity data are available for metabolites of pyridine. One metabolite, pyridine 1-oxide [pyridine *N*-oxide], was not mutagenic in *S. typhimurium* strains TA98 and TA100, and negative in tests for growth inhibition due to DNA damage in *Klebsiella pneumoniae* and *Escherichia coli* K12 (Voogd et al., 1980). Pyridine 1-oxide was also negative for growth inhibition resulting from DNA damage in *E. coli* and *Bacillus subtilis* (Nagao & Sugimura, 1972). These tests were all conducted in the absence of S9. Another metabolite, 3-pyridinol [3-hydroxypyridine], was not mutagenic in several strains of *S. typhimurium* tested with and without induced rat liver S9 (Florin et al., 1980). 2,5-Dihydroxypyridine (at 10–1000 μM) induced dose-dependent increases in DNA strand breaks in ϕX-174 phage DNA (Kim & Novak, 1990b), an effect that was mitigated in the presence of catalase, suggesting a role for oxidative damage in the production of DNA strand breaks. In this study, the structural analogue 3-hydroxypyridine (1 mM, single dose) did not induce DNA strand breaks (Kim & Novak, 1990b).

4.2.2 Other mechanisms

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

Chronic inflammation, fibrosis, and necrosis were seen in the liver of male and female F344/N rats and male Wistar rats exposed to pyridine at 0, 50, 100, 250, 500, or 1000 ppm in drinking-water for 13 weeks (NTP, 2000). Dose-related increases in hepatic fibrosis and necrosis were seen in male and female F344/N rats and male Wistar rats exposed to pyridine at 0, 100, 200, or 400 ppm in drinking-water for 2 years. Renal tubule hyperplasia was increased in the male F344/N rats given pyridine at 400 ppm (NTP, 2000).

In Sprague-Dawley rats, pyridine given at 100 or 150 mg/kg bw by intraperitoneal injection induced heme oxygenase-1 and CYP1A1 mRNA and protein in liver, lung, and kidney. Lipid peroxidation as assessed by thiobarbituric acid reactive substances increased in the liver, lung, and kidney (Iba et al., 1999). In male and female Syrian hamsters, pyridine given at 400 mg/kg bw by intraperitoneal injection increased CYP1A1, inducible nitric oxide synthase, and metallothionein I-II, responses indicative of the induction of oxidative stress (Tunca et al., 2009).

4.3 Data relevant to comparisons across agents and end-points

For the results of high-throughput screening assays of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013; EPA, 2016a, b; Filer et al., 2016), see Section 4.3 of the *Monograph* on 1-*tert*-butoxypropan-2-ol in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

Effects of pyridine include irritation of the eyes, skin, and respiratory tract (in the form of coughing and shortness of breath), as well as liver and kidney damage (Jori et al., 1983; ATSDR, 1992; OSHA, 2006).

4.5.2 Experimental systems

In a 2-year study in F344/N rats, dose-related non-neoplastic liver lesions, including centrilobular cytomegaly, cytoplasmic vacuolization, periportal fibrosis, fibrosis, centrilobular degeneration and necrosis, and pigmentation, were observed in both sexes. In male Wistar rats, a dose-related increase in non-neoplastic liver lesions, including centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation, was observed (NTP, 2000).

In male F344/N rats given pyridine at 500 and 1000 ppm in drinking-water for 13 weeks, increased incidences of kidney lesions, including casts, chronic inflammation, and mineralization, were observed. There was also a dose-related increase in the incidences of granular casts and hyaline degeneration (hyaline droplets), lesions consistent with α_{2u}-globulin nephropathy. There was no increase in non-neoplastic kidney lesions observed in Wistar rats (NTP, 2000).

IARC established seven criteria for the induction of kidney tumours to have occurred by an α_{2u}-globulin-associated response (Capen et al., 1999). Four criteria have been met for pyridine, specifically: (i) lack of genotoxic activity of the agent and/or metabolite (Section 4.2.1); (ii) male rat specificity for nephropathy and renal tumorigenicity (NTP, 2000); (iii) induction of the characteristic sequence of histopathological changes associated with α_{2u}-globulin accumulation (NTP, 2000); and (iv) identification of the accumulating protein as α_{2u}-globulin (α_{2u}-globulin protein was detected by immunohistochemistry; NTP, 2000). However, the remaining three of these criteria have not been met for pyridine, specifically: (i) reversible binding of the chemical or metabolite to α_{2u}-globulin (not measured); (ii) similarities in dose–response relationships of the tumour outcome with histopathological end-points associated with α_{2u}-globulin nephropathy (tumours occurred in the absence of α_{2u}-globulin; NTP, 2000); and (iii) induction of sustained increases in cell proliferation in the renal cortex (not measured).

5. Summary of Data Reported

5.1 Exposure data

Pyridine has several applications in organic chemistry and in industrial practice. It is a high production volume chemical. Pyridine can be formed from the breakdown of many natural materials in the environment. Due to its variety of applications, pyridine can be released in air, water, and soil. The major sources of exposure to pyridine for the general population are foods and cigarette smoke. Information about pyridine content in specific foods is scarce, but was

quantified in the volatile components of coffee and in fried or roasted food. The estimated pyridine intake in the USA was less than 1 g/year per person.

Occupational exposure may occur by inhalation and dermal contact during the production or use of pyridine as an intermediate or as a solvent. Exposure can also occur at coke ovens, oil-shale plants, and other similar industries. People working in quality control and research laboratories can also be exposed to pyridine.

5.2 Human carcinogenicity data

One small cohort study of mortality in workers exposed to pyridine and numerous other chemicals did not show any excess of mortality from cancer of the lung or all cancers combined. Six cases of squamous cell carcinoma of the skin were observed in the study population, but no risk data were reported.

5.3 Animal carcinogenicity data

In one well-conducted good laboratory practice (GLP) study in male and female mice given drinking-water containing pyridine, there was a significant increase, with a significant positive trend, in the incidence of hepatocellular adenoma, hepatocellular carcinoma, hepatoblastoma, and the combination of these tumours in males and females.

In another well-conducted GLP drinking-water study in male and female F344/N rats, pyridine significantly increased the incidence of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in males, and of mononuclear cell leukaemia in females, with a significant positive trend. In a third well-conducted GLP drinking-water study in male Wistar rats, pyridine significantly increased the incidence of testicular cell adenoma with a significant positive trend.

One study in male and female rats given pyridine by subcutaneous injection gave negative results. One feeding study and one skin-application study in transgenic mice gave negative results.

5.4 Mechanistic and other relevant data

Few data on absorption, distribution, metabolism, or excretion of pyridine in humans were available. Pyridine is absorbed following oral exposure in humans and other species, as well as by other routes in experimental animals. Pyridine *N*-oxide is the primary metabolite in humans and other species, and is generated through cytochrome P4502 E1-mediated oxidation. Pyridine induces multiple cytochrome P450s, and affects the metabolism and toxicity of other chemicals, such as carbon tetrachloride.

Regarding the key characteristics of carcinogens, there is *weak* evidence that pyridine is genotoxic. No human data are available. Pyridine did not induce chromosome or DNA damage in mice. It gave positive results in a few tests in *Drosophila melanogaster*, and in a single test of sister-chromatid exchange induction in Chinese hamster cells in the absence of metabolic activation from S9. Pyridine did not induce mutations in bacterial test systems.

There is *weak* evidence that pyridine induces oxidative stress. Two short-term studies in which pyridine was given by intraperitoneal injection, one in rats and one in hamsters, demonstrated oxidative stress. There is *moderate* evidence that pyridine induces chronic inflammation in rat liver from 13-week and chronic studies, in which necrosis and fibrosis were additionally shown. Renal tubule hyperplasia was observed in male rat kidney.

In the chronic drinking-water study in male rats, toxic effects and carcinogenicity were seen in the kidney. Three of the seven criteria established

by IARC for the induction of kidney tumours to have occurred by an α_{2u}-globulin-associated response have not been met.

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

Pyridine is *possibly carcinogenic to humans (Group 2B)*.

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