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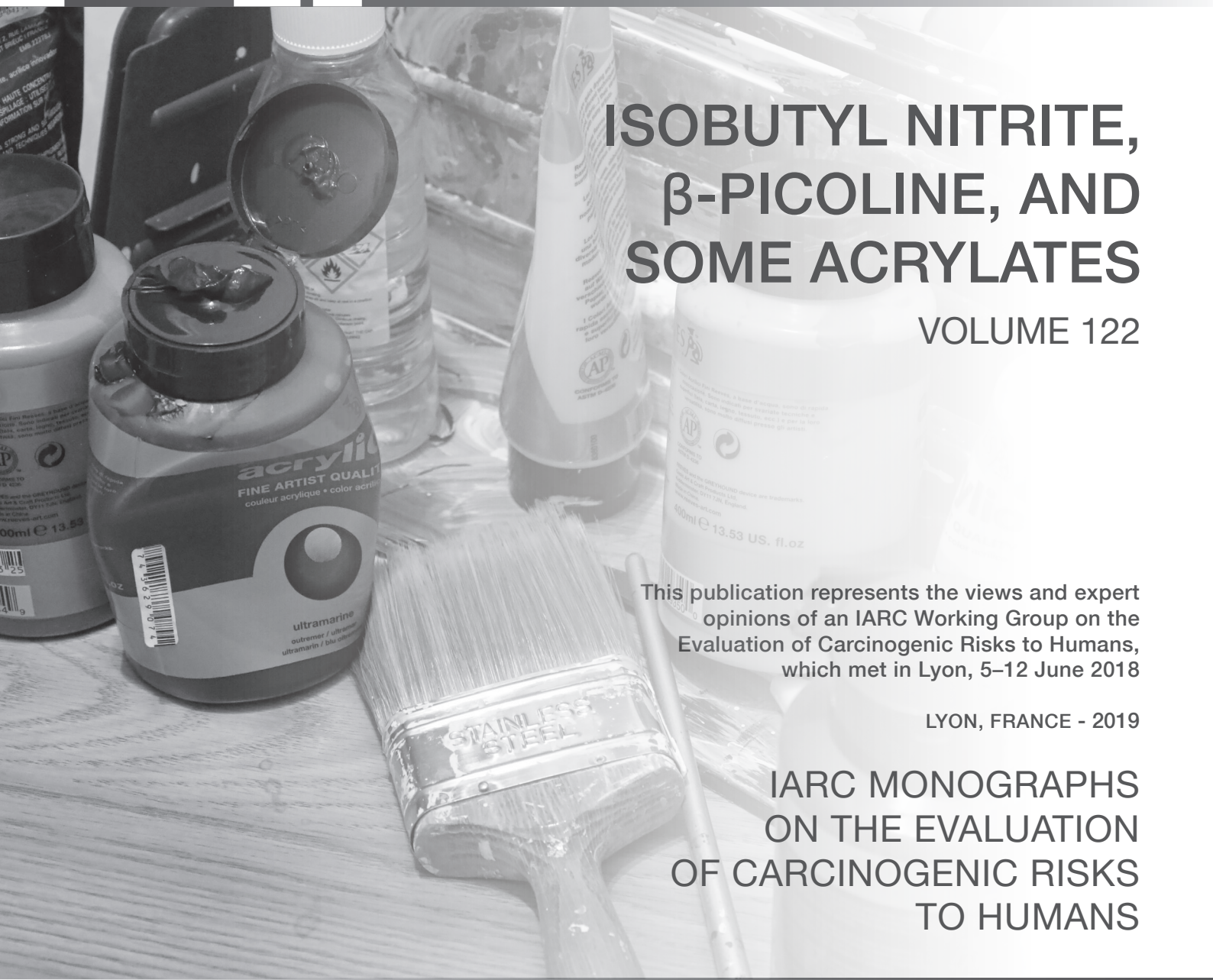

ISOBUTYL NITRITE, β-PICOLINE, AND SOME ACRYLATES

VOLUME 122

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International Agency for Research on Cancer

World Health Organization

β-PICOLINE

1. Exposure Data

1.1 Identification of the agent

See NTP (2014), HSDB (2015), Royal Society of Chemistry (2018)

1.1.1 Nomenclature

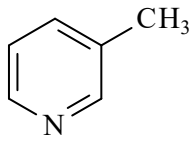
Chem. Abstr. Serv. Reg. No.: 108-99-6

Chem. Abstr. Serv. name: 3-methylpyridine

IUPAC systematic name: 3-methylpyridine

Synonyms: beta-picoline; 3-picoline; 3-mepy; pyridine; 3-methyl-; β-methylpyridine.

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: C_6H_7N

Relative molecular mass: 93.13

1.1.3 Chemical and physical properties

Description: β-picoline is a colourless liquid with a sweetish odour

Boiling point: 143–144 °C (experimental)

Melting point: –18 °C (experimental)

Flash point: 36 °C

Density: 0.9566 g/mL (at 20 °C)

Vapour pressure: 6.05 mm Hg [0.80 kPa] at 25 °C

Solubility: miscible with water at 20 °C; soluble in alcohol and ether, and very soluble in acetone

Conversion factor: 1 ppm = 3.81 mg/m^3 (at 1 atm and 25 °C).

1.1.4 Technical products and impurities

The industrial-scale fractionation of pyridine bases from coal tar is carried out by distillation; consequently, the β-picoline fraction may contain compounds with boiling points lower than 150 °C as principal components and small quantities of other alkylpyridines (e.g. 4-methylpyridine and 2-ethylpyridine). Commercial synthetic β-picoline is of high purity (> 90%), but may contain small quantities of other alkyl pyridines (Titon & Nardillo, 1995; NTP, 2014).

1.2 Production and use

1.2.1 Production process

β-Picoline, together with other pyridine bases, was originally isolated from pyrolysis of coal tar or coal gas. The isolation process is expensive; current production is mainly based on chemical synthesis (HSDB, 2015).

β-Picoline can be produced from the vapour-phase reaction of acetaldehyde and ammonia with formaldehyde and/or methanol in the presence of a catalyst, or from the vapour-phase reaction of acrolein with ammonia in the presence of an acid catalyst. It can also be produced from the vapour-phase reaction of 2-methylglutaronitrile over a nickel-containing catalyst in the presence of hydrogen to give 3-methylpiperidine, which then undergoes dehydrogenation over palladium-alumina to give β-picoline. Another method involves the reaction of cyclohexane and ammonia in the presence of zinc chloride (NTP, 2014; HSDB, 2015).

1.2.2 Production volume

β-Picoline is a chemical with a high production volume that is mainly produced in Asia, western Europe, and the USA (OECD, 2009). The major producers in Asia are China, including Taiwan, and India, and Japan (Scriven & Murugan, 2005). In China, total production of pyridine in thousands of metric tonnes was reported to be 14.1 in 2006, 19.3 in 2008, 50.5 in 2011, 80 in 2014, and 100 in 2016, representing an increase of sevenfold (Chinese Report, 2006, 2008, 2011, 2014, 2016). [Assuming a production ratio of 1:3 for β-picoline to total pyridines estimated by the Working Group, these would convert to about 4.7 (2006), 6.4 (2008), 16.8 (2011), 26.7 (2014), and 33.3 (2016) thousand metric tonnes of β-picoline.] In Europe, the annual production volume is estimated to be 100–1000 metric tonnes (ECHA, 2018). In the USA, reported annual production was about 21–29 million pounds (9.5–13.2 thousand metric tonnes) in 1998 (NTP, 2014) and 10–50 million pounds (4.5–22.7 thousand metric tonnes) in 2006 (HSDB, 2015).

1.2.3 Use

The major use of β-picoline is as a starting material for agrochemicals and pharmaceuticals. For example, it is used to make insecticides such as chlorpyrifos, herbicides such as fluazifop-butyl, and pharmaceuticals and/or dietary supplements such as niacin (vitamin B3) and its amide (Scriven & Murugan, 2005). It is also used as a solvent and intermediate in rubber accelerators, waterproofing agents, dyes, and resins (NTP, 2014; HSDB, 2015), as well as a flavouring substance in 31 food groups and beverages [Flavis (FL) No.: 14.135] (EFSA, 2006).

1.3 Analytical methods

β-Picoline can be determined by both gas and liquid chromatography methods (NTP, 2014). However, fewer methods based on liquid chromatography were reported for analysis of β-picoline, which may be attributed to its volatile nature. A summary of analytical methods reported for β-picoline is provided in Table 1.1.

1.4 Occurrence and exposure

1.4.1 Occurrence

β-Picoline can enter the environment through industrial wastewater due to its use as a starting material and intermediate in various industries (Scriven & Murugan, 2005). It is present in effluents from the manufacture and use of coal-derived liquid fuels and from the disposal of coal liquefaction and gasoline waste by-products (NTP, 2014). β-Picoline is also released into air as a result of cigarette smoking (Kurgat et al., 2016).

(a) Water

β-Picoline was detected at concentrations of 1.23, 0.30, 0.20, and 0.01 mg/L at depths of 6.1, 3.3, 5.8, and 11.0 m, respectively, in groundwater samples collected from two different sites

Table 1.1 Representative methods for the analysis of β-picoline

Sample matrix	Assay procedure	Limit of detection	Reference
Water, sediment	GC-EI/MS	0.01 ng on column	Tsukioka & Murakami (1987)
Air, cigarette smoke	GC-EI/MS	0.005–0.010 ng on column	Llompart et al. (1998), Kulshreshtha & Moldoveanu (2003)
Air, exhaled breath of tobacco cigarette and electronic cigarette smokers	TD-GC/MS	5 ng/m^3, 0.16–1.60 ng per sample	Heavner et al. (1992), Vainiotalo et al. (2008), Marco & Grimalt (2015)
Cigarette smoke	RP-HPLC/UV	0.5–1.0 µg/L	Esrafili et al. (2012)
Water, urine	RP-HPLC/UV	2.5, 7.3 µg/L	Shahdousti et al. (2015)

EI, electron ionization; GC, gas chromatography; HPLC, high-performance liquid chromatography; MS, mass spectrometry; RP, reversed phase; TD, thermal desorption; UV, ultraviolet spectroscopy

in Pensacola Bay, Florida, USA. The sites were heavily contaminated with creosote, a complex distillate from coal tar used for wood preserving (Goerlitz, 1992). Middaugh et al. (1991) reported concentrations of 0.0007 and 0.1 mg/L of β-picoline in surface and groundwater samples, respectively, collected from the same contaminated area. Stuermer et al. (1982) reported combined concentrations of β- and γ-picoline (4-methylpyridine) of 0.00069–0.05100 mg/L in three groundwater samples collected near two underground coal gasification sites in north-eastern Wyoming, USA. β-Picoline was detected, but not quantified, in a survey of drinking-water samples from United States cities including Cincinnati (Ohio), Miami (Florida), New Orleans (Louisiana), Ottumwa (Iowa), Philadelphia (Pennsylvania), and Seattle (Washington) (EPA, 1984). β-Picoline was also detected at a concentration of 6.5 mg/L in oil shale condensate retort water samples collected from the Logan Wash site, Colorado, USA, in 1979 (Leenheer et al., 1982).

(b) Air

β-Picoline is a component of tobacco smoke, and was detected in cigarette smoke with emission factors of 12–36 µg per cigarette (Singer et al., 2002). The median concentration of β-picoline in indoor air samples collected in 1991 from the homes of smokers (0.58 µg/m^3, n = 25) in Columbus, Ohio, USA, exceeded that from the homes of non-smokers (0.16 µg/m^3, n = 24) (Heavner et al., 1995). Higher levels of β-picoline were also detected in air samples collected from the smoking areas of 10 Finnish restaurants (median, 1.4 µg/m^3) compared with the non-smoking areas (median, 0.18 µg/m^3) (Vainiotalo et al., 2008). β-Picoline was not detected in an urban air sample from Boulder, Colorado, USA, and in a rural air sample from an undeveloped area of the oil shale region (Hawthorne & Sievers, 1984).

(c) Diet

β-Picoline was reported to occur naturally in coffee (1.3 mg/kg), beer (0.0008 mg/kg), and whisky (< 0.0006 mg/kg) (EFSA, 2006), and was detected in three types of fermented soya bean curd from Hong Kong Special Administrative Region, China, with concentrations in the range 18–55 µg/kg (Chung, 1999b). It was also found in edible crab (*Charybdis feriatus*) collected from Hong Kong Special Administrative Region, with concentrations of 14.6, 11.6, and 7.5 µg/kg in carapace, leg, and body meat, respectively (Chung, 1999a). β-Picoline was identified, but not quantified, in boiled beef (Golovnya et al., 1979) and mutton samples (Shahidi et al., 1986). It is also used as a flavouring agent in 31 food groups including dairy products, processed fruits, meat and meat products, and fish and fish products (EFSA, 2006).

1.4.2 Exposure

(a) Exposure of the general population

Non-occupational exposure can occur via inhalation of contaminated air, ingestion of contaminated food and water, and dermal contact with products containing β-picoline (HSDB, 2015). A study by the European Food Safety Authority estimated the maximized survey-derived daily intake and the modified theoretical added maximum daily intake for β-picoline (3-methylpyridine) from its intake as a flavouring substance at 0.027 and 380 μg per person per day, respectively. Both estimates fell short of the reported threshold of concern (540 μg per person per day; EFSA, 2006).

(b) Occupational exposure

Occupational exposure occurs primarily through inhalation or dermal contact during the production and/or use of β-picoline (HSDB, 2015). Between 1981 and 1983, the number of employees occupationally exposed to β-picoline in the USA was estimated by the United States National Institute for Occupational Safety and Health as 5202, of which 390 were women (NIOSH, 1985). Hawthorne & Sievers (1984) reported concentrations of combined β-picoline and γ-picoline (4-methylpyridine) in air samples collected in and near the shale oil wastewater treatment facility at the Logan Wash site, Colorado, in 1982. A higher concentration was measured indoors at the workbench of the operator near the activated sludge tank (35 μg/m^3) compared with that measured outdoors (8 μg/m^3).

1.5 Regulations and guidelines

No specific occupational exposure limits for β-picoline were available to the Working Group. The American Industrial Hygiene Association derived a workplace environmental exposure limit of 2 ppm for picolines as an 8-hour time-weighted average (TWA) and a short-term exposure limit of 5 ppm for a 15-minute TWA (Myers, 2013). These exposure limits included a skin notation.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

Drinking-water

Groups of 50 male and 50 female B6C3F$_1$/N mice (age, 5–6 weeks) were given drinking-water containing β-picoline (purity, 96.4%) at a concentration of 0, 312.5, 625, or 1250 mg/L ad libitum for 7 days per week for 105 weeks (NTP, 2014). Average daily doses of β-picoline were approximately 0, 26, 50, and 92 mg/kg body weight (bw) for males and 0, 18, 37, and 68 mg/kg bw for females. Survival of all exposed groups was similar to that of the control groups. However, there was a small but significant positive trend in the survival of males with increasing exposure. Mean body weights of males exposed at the highest dose were at least 10% less than those of the control group after week 57, and body weights of females exposed at the highest dose were generally 10% less after week 13. Water consumption was lower in males exposed at the intermediate and highest doses and females exposed at the highest dose compared with those in the controls after the first 13 weeks of the study.

The incidence of hepatocellular carcinoma (includes multiple) (11/49, 20/50, 26/50, and 23/50) and of hepatocellular carcinoma or hepatoblastoma (combined) (12/49, 21/50, 28/50, and 24/50) was significantly increased in all exposed

Table 3.1 Studies of carcinogenicity with β-picoline in experimental animals

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	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (M) 5–6 wk 105 wk NTP (2014)	Drinking-water β-Picoline, 96.4% Tap water 0, 312.5, 625, 1250 mg/L ad libitum 50, 50, 50, 50 24, 26, 27, 33	*Lung* Bronchioloalveolar adenoma 6/50 (12%), 11/50 (22%), 16/50* (32%), 8/50 (16%)	*P = 0.037, poly-3 test	Principal strengths: well-conducted GLP study Historical incidence (mean ± SD; range): 2-yr drinking-water studies with untreated control groups, 21/100 (21.0 ± 12.7%; 12–30%); all routes, 172/1150 (15.0 ± 6.9%; 2–30%)
Full carcinogenicity Mouse, B6C3F$_1$/N (F) 5–6 wk 105 wk NTP (2014)	Drinking-water β-Picoline, 96.4% Tap water 0, 312.5, 625, 1250 mg/L ad libitum 50, 50, 50, 50 38, 32, 35, 33	*Liver* Hepatocellular carcinoma 11/49 (22%), 20/50* (40%), 26/50** (52%), 23/50*** (46%)	P = 0.006 (trend), *P = 0.031, **P < 0.001, ***P = 0.005; poly-3 test	Principal strengths: well-conducted GLP study Historical incidence (mean ± SD; range): Hepatocellular adenoma (includes multiple): drinking-water, 52/98 (53.1 ± 34.6%; 29–78%); all routes, 380/1195 (31.8 ± 21.4%; 2–78%) Hepatocellular carcinoma (includes multiple): drinking-water, 19/98 (19.4 ± 4.3%; 16–22%); all routes, 144/1195 (12.1 ± 10.8%; 0–46%) Hepatoblastoma (includes multiple): drinking-water, 1/98 (1.0 ± 1.4%; 0–2%); all routes, 4/1195 (0.3 ± 0.8%; 0–2%) Hepatocellular carcinoma or hepatoblastoma (combined): drinking-water, 20/98 (20.4 ± 5.8%; 16–24%); all routes, 148/1195 (12.4 ± 11.2%; 0–46%) Bronchioloalveolar carcinoma (includes multiple): drinking-water, 9/100 (9.0 ± 7.1%; 4–14%); all routes, 44/1196 (3.7 ± 3.3%; 0–14%) Bronchioloalveolar adenoma or carcinoma (combined): drinking-water, 13/100 (13.0 ± 12.7%; 4–22%); all routes, 100/1196 (8.4 ± 4.3%; 2–22%) Significant increase in the incidence of hyperplasia of the alveolar epithelium in females at the highest dose
		Hepatoblastoma 1/49 (2%), 3/50 (6%), 4/50 (8%), 4/50 (8%)	NS	
		Hepatocellular carcinoma or hepatoblastoma (combined) 12/49 (24%), 21/50* (42%), 28/50** (56%), 24/50*** (48%)	P = 0.005 (trend), *P = 0.033, **P < 0.001, ***P = 0.005; poly-3 test	
		Hepatocellular adenoma 38/49 (78%), 46/50* (92%), 46/50 (92%), 39/50 (78%)	*P = 0.025, poly-3 test	
		Lung Bronchioloalveolar adenoma (includes multiple) 5/50 (10%), 6/50 (12%), 4/49 (8%), 11/50 (22%)	P = 0.046 (trend), poly-3 test	
		Bronchioloalveolar carcinoma (includes multiple) 7/50 (14%), 8/50 (16%), 10/49 (20%), 13/50 (26%)	NS	

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	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (F) 5–6 wk 105 wk NTP (2014) (cont.)		Bronchioloalveolar adenoma or carcinoma (combined) 11/50 (22%), 13/50 (26%), 13/49 (27%), 21/50* (42%) Bronchioloalveolar adenoma (multiple) 0/50, 1/50 (2%), 0/49, 1/50 (2%) Bronchioloalveolar carcinoma (multiple) 0/50, 2/50 (4%), 2/49 (4%), 4/50 (8%)	$P = 0.015$ (trend), $^*P = 0.022$; poly-3 test NS NS	
Full carcinogenicity Rat, F344/N (M) 6–7 wk 104 wk NTP (2014)	Drinking-water β-Picoline, 96.4% Tap water 0, 156.25, 312.5, 625 mg/L ad libitum 50, 50, 50, 50 33, 31, 32, 24	*Lung* Bronchioloalveolar carcinoma 0/50, 0/50, 4/50 (8%), 2/50 (4%) Bronchioloalveolar adenoma or carcinoma (combined) 3/50 (6%), 5/50 (10%), 5/50 (10%), 4/50 (8%) Bronchioloalveolar adenoma 3/50 (6%), 5/50 (10%), 1/50 (2%), 2/50 (4%)	 NS NS NS	Principal strengths: well-conducted GLP study Historical incidence (mean ± SD; range): Bronchioloalveolar carcinoma (includes multiple): drinking-water, 0/100; all routes, 15/1249 (1.2 ± 1.4%; 0–6%) Bronchioloalveolar adenoma or carcinoma (combined): drinking-water, 7/100 (7.0 ± 1.4%; 6–8%); all routes, 45/1249 (3.6 ± 2.8%; 0–10%)
Full carcinogenicity Rat, F344/N (F) 6–7 wk 105 wk NTP (2014)	Drinking-water β-Picoline, 96.4% Tap water 0, 156.25, 312.5, 625 mg/L ad libitum 50, 50, 50, 50 30, 32, 33, 30	*Lung* Bronchioloalveolar adenoma 0/50, 3/50 (6%), 2/50 (4%), 5/50* (10%) Bronchioloalveolar carcinoma 0/50, 1/50 (2%), 0/50, 0/50 Bronchioloalveolar adenoma or carcinoma (combined) 0/50, 4/50 (8%), 2/50 (4%), 5/50* (10%)	 $P = 0.029$ (trend), $^*P = 0.030$; poly-3 test NS $P = 0.050$ (trend), $^*P = 0.030$; poly-3 test	Principal strengths: well-conducted GLP study Historical incidence (mean ± SD; range): Bronchioloalveolar adenoma: drinking-water, 4/100 (4.0 ± 5.7%; 0–8%); all routes, 25/1200 (2.1 ± 2.9%; 0–8%) Bronchioloalveolar adenoma or carcinoma (combined): drinking-water, 4/100 (4.0 ± 5.7%; 0–8%); all routes, 27/1200 (2.3 ± 2.9%; 0–8%) Bronchioloalveolar carcinoma: drinking-water, 0/100; all routes, 3/1200 (0.3 ± 0.7%; 0–2%)

F, female; GLP, good laboratory practice; M, male; NS, not significant; SD, standard deviation; wk, week; yr, year

groups of female mice, with a significant positive trend. There was also a significant increase in the incidence of hepatocellular adenoma (includes multiple) (38/49, 46/50, 46/50, and 39/50) in female mice exposed at the lowest dose. Hepatoblastoma [a rare neoplasm in this strain of female mice] occurred in 1/49 (2%) control and 3/50 (6%), 4/50 (8%), and 4/50 (8%) exposed females; incidence in all the treated groups exceeded the upper bound of the range for historical controls for drinking-water studies (range, 0–2%) and for all routes of administration (range, 0–2%). The lung was also a target organ in female mice. The incidence of bronchioloalveolar adenoma or carcinoma (combined) (11/50, 13/50, 13/49, and 21/50) in females exposed at the highest dose was significantly increased compared with that in controls, with a significant positive trend. There was also a [non-statistically significant] dose-dependent association between exposure and the incidence of bronchioloalveolar carcinoma (includes multiple) (7/50, 8/50, 10/49, and 13/50). Additionally, multiple bronchioloalveolar adenomas and multiple bronchioloalveolar carcinomas occurred [non-statistically significant] in most of the exposed groups of females, but no multiple lung neoplasms occurred in the controls. In male mice, there was a significant increase in the incidence of bronchioloalveolar adenoma (includes multiple) (6/50, 11/50, 16/50, and 8/50) in the group exposed at the intermediate dose. [The Working Group noted that this was a well-conducted study that complied with good laboratory practice (GLP).]

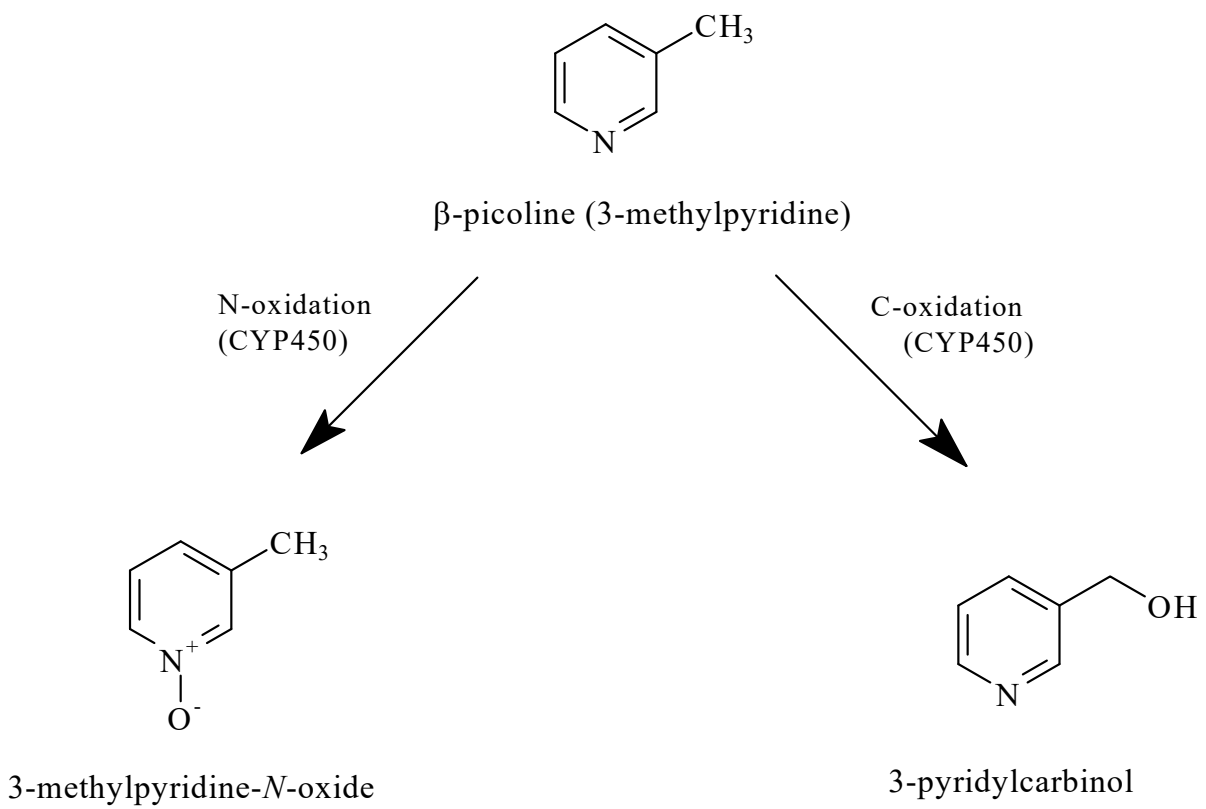
3.2 Rat

Drinking-water

Groups of 50 male and 50 female Fischer 344/N rats (age, 6–7 weeks) were given drinking-water containing β-picoline (purity, 96.4%) at concentrations of 0, 156.25, 312.5, or 625 mg/L ad libitum for 7 days per week for 104 weeks (males) and 105 weeks (females) (NTP, 2014). Average daily doses of β-picoline were approximately 0, 6, 12, and 22 mg/kg bw (males), and 0, 7, 14, and 26 mg/kg bw (females). The survival of exposed groups of male and female rats was similar to that of the control groups. Mean body weights were slightly less than those of controls throughout the study for males exposed at the highest dose, and were 10% less at the end of the study. Mean body weights were slightly less than those of controls for most of the study for females exposed at the highest dose, and were 9% less for a 16-week period towards the end of the study. Decreased water consumption was evident in males and females exposed at the highest dose compared with that of the controls throughout the study.

Bronchioloalveolar adenomas were observed in all exposed groups of female rats, but not in controls, with an incidence of 0/50, 3/50 (6%), 2/50 (4%), and 5/50 (10%), respectively; there was a significant positive trend in the incidence of this neoplasm and a significant increase in the incidence in females exposed at the highest dose that exceeded the upper bound of the range for historical controls for drinking-water studies (range, 0–8%) and for all routes of administration (range, 0–8%). One bronchioloalveolar carcinoma occurred in a female exposed at the lowest dose. Bronchioloalveolar carcinoma occurred in males exposed at the intermediate dose (4/50) [non-statistically significant] and highest dose (2/50) [non-statistically significant], but not at the lowest dose or in controls. However, the incidence of bronchioloalveolar adenoma or carcinoma (combined) in males was similar between the control and exposed groups and was also consistent with the historical incidence of this combination of tumours in male Fischer 344 rats. [The Working Group noted that this was a well-conducted study that complied with GLP.]

Fig. 4.1 Proposed metabolic pathways of β-picoline



CYP450, cytochrome P450
Compiled by the Working Group

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

No data were available on the absorption, distribution, metabolism, and excretion to the Working Group.

4.1.2 Experimental systems

See Fig. 4.1

Few data were available on the absorption, distribution, metabolism, and excretion of β-picoline. It is readily absorbed from the gastrointestinal tract, intraperitoneal cavity, and the lungs, and moderately well absorbed through the skin (Trochimowicz et al., 2001).

Gorrod & Damani (1979a) investigated the metabolism of β-picoline in vitro using various organ homogenates of rabbits, guinea-pigs, and rats. β-Picoline is metabolized in mice, rats, hamsters, guinea-pigs, and rabbits through the C-oxidation and N-oxidation metabolic pathways (yielding 3-pyridylcarbinol and 3-methylpyridine-*N*-oxide, respectively), with the maximum activity being found in the liver and lung (Gorrod & Damani, 1979a). In a separate study, Gorrod & Damani (1979b) showed that these C-oxidation and N-oxidation reactions of β-picoline are mediated by a cytochrome P450 (CYP450) system, as shown by the reduced

Table 4.1 Genetic and related effects of β-picoline in experimental systems

Test system	End-point	Results[a]		Concentration (HIC or LEC)	Reference
		Without metabolic activation	With metabolic activation		
Mouse, B6C3F$_1$ (M, F); peripheral blood erythrocytes	Micronucleus formation	–	NA	78–1250 mg/L, drinking-water, for 3 mo	NTP (2014)
Salmonella typhimurium TA98	Reverse mutation	NT	–	1000 µg/plate	Ho et al. (1981)
Salmonella typhimurium TA98, TA100, TA1535, TA1537	Reverse mutation	–	–	8540 µg/plate	Haworth et al. (1983)
Salmonella typhimurium TA97, TA98, TA100, TA102	Reverse mutation	–	–	5000 µg/plate	Claxton et al. (1987)

F, female; HIC, highest ineffective concentration; LEC, lowest effective concentration; M, male; mo, month; NA, not applicable; NT, not tested
[a] –, negative; the level of significance was set at $P < 0.005$ in all cases

C-oxidation and N-oxidation in the presence of CYP450 inhibitors.

The existence of the N-oxidation pathway of β-picoline was also demonstrated in rodents in vivo. This was shown by the presence of 3-methyl-*N*-oxide at concentrations of 6.6% and 4.2% in urine of mice and rats at 72 hours after intraperitoneal injection of β-picoline at 40 mg/kg bw (Gorrod & Damani, 1980).

4.1.3 Modulation of metabolic enzymes

In female Fischer 344 rats given drinking-water containing β-picoline at concentrations of 156, 312, 625, and 1250 mg/L for 23 days, a statistically significant dose-dependent increase in the activity of hepatic 7-pentoxyresorufin-*O*-dealkylase, a marker for CYP2B1, was observed (NTP, 2014). A similar effect on 7-pentoxyresorufin-*O*-dealkylase activity was also observed in the livers of male Fischer 344 rats exposed to β-picoline at 312, 625, and 1250 mg/L (NTP, 2014).

4.2 Mechanisms of carcinogenesis

This section summarizes the available evidence for the key characteristics of carcinogens (Smith et al., 2016). Data were available only for the key characteristic "is genotoxic"; for the other key characteristics of human carcinogens, insufficient data were available for evaluation.

4.2.1 Genetic and related effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

See Table 4.1

In male and female B6C3F$_1$ mice given drinking-water containing β-picoline at concentrations of 78–1250 mg/L for 3 months, no increase in the frequency of micronucleus formation in peripheral blood erythrocytes was observed (NTP, 2014).

Several studies investigated the mutagenicity of β-picoline in the Ames test. β-Picoline did not induce mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA102 at concentrations of up to 5000 µg per plate (Claxton et al.,

1987; NTP, 2014) or in strains TA98, TA100, TA1535, or TA1537 at concentrations of up to 8540 μg per plate (Haworth et al., 1983; NTP, 2014). Ho et al. (1981) also reported negative results for the induction of gene mutation in *S. typhimurium* strain TA98 tested with β-picoline at concentrations of up to 1000 μg per plate.

4.2.2 Other mechanistic data

No data were available to the Working Group.

4.3 Other adverse effects

In male Fischer 344 rats given drinking-water containing β-picoline at a concentration of 312, 625, or 1250 mg/L for 3 months, a significant increase in the concentration of α_{2u}-globulin in the kidney was observed. This increase was accompanied by progressive nephropathy in rats at 625 and 1250 mg/L, and hyaline droplet accumulation in proximal renal tubules in rats at 1250 mg/L (NTP, 2014). Neurotoxicological effects were also observed in rats (Dyer et al., 1985).

4.4 Data relevant to comparisons across agents and end-points

See the monograph on isobutyl nitrite in the present volume.

5. Summary of Data Reported

5.1 Exposure data

β-Picoline, a methylpyridine, is a "high production volume" chemical that is produced globally. A large increase in the production volume has been observed in China during the last decade. β-Picoline is widely used as a starting material for agrochemicals (e.g. chlorpyrifos) and pharmaceuticals (e.g. vitamin B3). It is also used as a solvent and intermediate in rubber accelerators, waterproofing agents, dyes, and resins, and as a flavouring substance in foods and beverages. β-Picoline is released to the environment through industrial wastewater and as a result of cigarette smoking. It also occurs naturally at very low concentrations in coffee, beer, and whisky. Occupational exposure occurs primarily through inhalation or dermal contact during the production or use of β-picoline. Exposure of the general population can occur via inhalation of tobacco smoke, ingestion of contaminated food or water, or dermal contact with products containing β-picoline.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

β-Picoline was tested for carcinogenicity in one well-conducted good laboratory practice (GLP) 2-year drinking-water study in male and female mice, and in one well-conducted GLP 2-year drinking-water study in male and female rats.

β-Picoline caused a significant increase in the incidence of hepatocellular carcinoma and of hepatocellular carcinoma or hepatoblastoma (combined) in all exposed female mice compared with controls, with a significant positive trend. There was also a significant positive trend in the incidence of hepatocellular adenoma in female mice. There was a significant positive trend in the incidence of bronchioloalveolar adenoma of the lung in female mice. The incidence of bronchioloalveolar adenoma or carcinoma (combined) in female mice exposed at the highest dose was also significantly increased compared with that in controls, with a significant positive trend. There

was a significant increase in the incidence of bronchioloalveolar adenoma in male mice.

β-Picoline caused a significant increase in the incidence of bronchioloalveolar adenoma in female rats exposed at the highest dose, with a significant positive trend. In male rats, there was no significant increase in the incidence of any tumour.

5.4 Mechanistic and other relevant data

No data on the absorption, distribution, metabolism, and excretion of β-picoline in exposed humans were available. In rodents, β-picoline is readily absorbed from the gastrointestinal tract, intraperitoneal cavity, and the lungs, moderately well absorbed through the skin, and metabolized by cytochrome P450-mediated N-oxidation. An additional C-oxidation pathway has been demonstrated in various organ homogenates. In the Fischer 344 rat, β-picoline induced a dose-dependent increase in hepatic 7-pentoxyresorufin-*O*-dealkylase activity.

Regarding the key characteristics of carcinogens, β-picoline gave negative results in the mouse micronucleus test and in the Ames assay. No other relevant data were available, including from humans or human experimental systems.

In male Fischer 344 rats exposed for 3 months, β-picoline significantly increased the level of α_{2u}-globulin in the kidney.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of β-picoline.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of β-picoline.

6.3 Overall evaluation

β-Picoline is *not classifiable as to its carcinogenicity to humans (Group 3).*

References

Chinese Report (2006). Total pyridine production. Official reports extracted and translated from: http://www.docin.com/p-1463260050.html [Chinese]

Chinese Report (2008). Total pyridine production. Official reports extracted and translated from: http://www.doc88.com/p-3854516048984.html [Chinese]

Chinese Report (2011). Total pyridine production. Official reports extracted and translated from: http://www.ebrun.com/20130108/65037.shtml [Chinese] [web link broken]

Chinese Report (2014). Total pyridine production. Official reports extracted and translated from: http://www.tendencichem.com/news_detail_cn/id/38.html [Chinese] [web link broken]

Chinese Report (2016). Total pyridine production. Official reports extracted and translated from: http://www.yuecai.com/c/2016-08-02/264612.shtml [Chinese] [web link broken]

Chung HY (1999a). Volatile components in crabmeats of *Charybdis feriatus*. *J Agric Food Chem*, 47(6):2280–7. doi:10.1021/jf981027t PMID:10794623

Chung HY (1999b). Volatile components in fermented soybean (Glycine max) curds. *J Agric Food Chem*, 47(7):2690–6. doi:10.1021/jf981166a PMID:10552546

Claxton LD, Dearfield KL, Spanggord RJ, Riccio ES, Mortelmans K (1987). Comparative mutagenicity of halogenated pyridines in the *Salmonella typhimurium*/mammalian microsome test. *Mutat Res*, 176(2):185–98. doi:10.1016/0027-5107(87)90049-2 PMID:3543664

Dyer RS, Burdette LJ, Janssen R, Boyes WK (1985). Neurophysiological consequences of acute exposure to methylpyridines. *Fundam Appl Toxicol*, 5(5):920–32. doi:10.1016/0272-0590(85)90174-5 PMID:4065464

ECHA (2018). REACH dossier for 3-methylpyridine. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/registration-dossier/-/registered-dossier/2119/1

EFSA (2006). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission related to Flavouring Group Evaluation 24: Pyridine, pyrrole, indole and quinoline derivatives from chemical group 28 (Commission Regulation (EC) No 1565/2000 of 18 July 2000). *EFSA J*, 372:1–63. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/372.

EPA (1984). GC/MS Analysis of organics in drinking water concentrates and advanced waste treatment concentrates: Volume 1. EPA-600/1-84-020A (NTIS PB85-128239). Available from: https://nepis.epa.gov/Exe/ZyPDF.cgi/9100A600.PDF?Dockey=9100A600.PDF, accessed 27 February 2018.

Esrafili A, Yamini Y, Ghambarian M, Ebrahimpour B (2012). Automated preconcentration and analysis of organic compounds by on-line hollow fiber liquid-phase microextraction-high performance liquid chromatography. *J Chromatogr A*, 1262:27–33. doi:10.1016/j.chroma.2012.09.003 PMID:22999199

Goerlitz DF (1992). Site investigations: a review of studies of contaminated groundwater conducted by the U.S. geological survey organics project, Menlo Park, California, 1961-1990. In: Lesage S, Jackson RE, editors. Groundwater contamination and analysis at hazardous waste sites. New York, USA: Marcel Dekker Inc; pp. 295–355.

Golovnya RV, Zhuravleva IL, Kapustin JP (1979). Gas-chromatographic analysis of volatile nitrogen bases of boiled beef as possible precursors of *N*-nitrosamines. *Chem Senses*, 4(2):97–105. doi:10.1093/chemse/4.2.97

Gorrod JW, Damani LA (1979a). Some factors involved in the N-oxidation of 3-substituted pyridines by microsomal preparations in vitro. *Xenobiotica*, 9(4):209–18. doi:10.3109/00498257909038723 PMID:483857

Gorrod JW, Damani LA (1979b). The effect of various potential inhibitors, activators and inducers on the N-oxidation of 3-substituted pyridines in vitro. *Xenobiotica*, 9(4):219–26. doi:10.3109/00498257909038724 PMID:483858

Gorrod JW, Damani LA (1980). The metabolic N-oxidation of 3-substituted pyridines in various animal species in vivo. *Eur J Drug Metab Pharmacokinet*, 5(1):53–7. doi:10.1007/BF03189445 PMID:7389753

Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E (1983). Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen*, 5(Suppl 1):1–142. doi:10.1002/em.2860050703 PMID:6365529

Hawthorne SB, Sievers RE (1984). Emission of organic air pollutants from shale oil wastewaters. *Environ Sci Technol*, 18(6):483–90. doi:10.1021/es00124a016 PMID:22247953

Heavner DL, Morgan WT, Ogden MW (1995). Determination of volatile organic compounds and ETS apportionment in 49 homes. *Environ Int*, 21(1):3–21. doi:10.1016/0160-4120(94)00018-3

Heavner DL, Ogden MW, Nelson PR (1992). Multisorbent thermal-desorption gas chromatography/mass selective detection method for the determination of target volatile organic-compounds in indoor air. *Environ Sci Technol*, 26(9):1737–46. doi:10.1021/es00033a004

Ho CH, Clark BR, Guerin MR, Barkenbus BD, Rao TK, Epler JL (1981). Analytical and biological analyses of test materials from the synthetic fuel technologies. IV. Studies of chemical structure – mutagenic activity relationships of aromatic nitrogen compounds relevant to synfuels. *Mutat Res*, 85(5):335–45. doi:10.1016/0165-1161(81)90224-7 PMID:7029261

HSDB (2015). 3-Methylpyridine (CAS No. 108-99-6). Hazardous Substances Data Bank [online database]. Toxicology Data Network. Bethesda (MD), USA: United States National Library of Medicine. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+4254, accessed 27 February 2018.

Kulshreshtha NP, Moldoveanu SC (2003). Analysis of pyridines in mainstream cigarette smoke. *J Chromatogr A*, 985(1-2):303–12. doi:10.1016/S0021-9673(02)01472-3 PMID:12580498

Kurgat C, Kibet J, Cheplogoi P (2016). Molecular modeling of major tobacco alkaloids in mainstream cigarette smoke. *Chem Cent J*, 10(1):43 doi:10.1186/s13065-016-0189-5 PMID:27429644

Leenheer JA, Noyes TI, Stuber HA (1982). Determination of polar organic solutes in oil-shale retort water. *Environ Sci Technol*, 16(10):714–23. doi:10.1021/es00104a015

Llompart M, Li K, Fingas M (1998). Headspace solid-phase microextraction for the determination of volatile and semi-volatile pollutants in water and air. *J Chromatogr A*, 824(1):53–61. doi:10.1016/S0021-9673(98)00613-X PMID:9818428

Marco E, Grimalt JO (2015). A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic cigarette smokers. *J Chromatogr A*, 1410:51–9. doi:10.1016/j.chroma.2015.07.094 PMID:26243705

Middaugh DP, Mueller JG, Thomas RL, Lantz SE, Hemmer MH, Brooks GT, et al. (1991). Detoxification of pentachlorophenol and creosote contaminated groundwater by physical extraction: chemical and biological assessment. *Arch Environ Contam Toxicol*, 21(2):233–44. doi:10.1007/BF01055342 PMID:1958078

Myers J (2013). WEEL values (2011). In: ERPG/WEEL Handbook. Falls Church (VA), USA: American Industrial Hygiene Association Guideline Foundation; pp. 43–50. Available from: https://www.tera.org/OARS/OARS%20WEELs%20July%202013.pdf, accessed 14 October 2019.

NIOSH (1985). National Occupational Exposure Survey conducted from 1981-1983. Estimated numbers of employees potentially exposed to specific agents by 2-digit standard industrial classification (SIC).

National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/noes/, accessed 27 February 2018.

NTP (2014). Toxicology and carcinogenesis studies of β-picoline (CAS No. 108-99-6) in F344/N rats and B6C3F$_1$/N mice (drinking water studies). *Natl Toxicol Program Tech Rep Ser*, 580:1–172.

OECD (2009). The 2007 OECD list of high production volume chemicals. Series on testing and assessment. Number 112. Available from: http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm, accessed 14 October 2019.

Royal Society of Chemistry (2018). ChemSpider Search and Share chemistry. London, United Kingdom: Royal Society of Chemistry. Available from: http://www.chemspider.com, accessed 21 February 2018.

Scriven EFV, Murugan R, editors (2005). Pyridine and pyridine derivatives. Kirk-Othmer Encyclopedia of Chemical Technology. New York (NY), USA: John Wiley and Sons.

Shahdousti P, Aghamohammadi M, Seidi S, Harooni B, Kalhor H (2015). Monitoring of pyridine, 3-picoline and quinoline in smokers' urine using ultrasound-assisted emulsification microextraction coupled with high-performance liquid chromatography. *J Iranian Chem Soc*, 12(10):1757–63. doi:10.1007/s13738-015-0650-8

Shahidi F, Rubin LJ, D'Souza LA (1986). Meat flavor volatiles: a review of the composition, techniques of analysis, and sensory evaluation. *Crit Rev Food Sci Nutr*, 24(2):141–243. doi:10.1080/10408398609527435 PMID:3527563

Singer BC, Hodgson AT, Guevarra KS, Hawley EL, Nazaroff WW (2002). Gas-phase organics in environmental tobacco smoke. 1. Effects of smoking rate, ventilation, and furnishing level on emission factors. *Environ Sci Technol*, 36(5):846–53. doi:10.1021/es011058w PMID:11918006

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. doi:10.1289/ehp.1509912 PMID:26600562

Stuermer DH, Ng DJ, Morris CJ (1982). Organic contaminants in groundwater near an underground coal gasification site in northeastern Wyoming. *Environ Sci Technol*, 16(9):582–7. doi:10.1021/es00103a009 PMID:22284199

Titon MC, Nardillo AM (1995). Separation of low-boiling pyridine bases by gas chromatography. *J Chromatogr A*, 699(1-2):403–7. doi:10.1016/0021-9673(95)00085-2

Trochimowicz HJ, Kennedy GL, Krivanek ND (2001). Alkylpyridines and miscellaneous organic nitrogen compounds. In: Bingham E, Cohrssen B, Powell CH, editors. Patty's Toxicology. Volume 4. 5th ed. Hoboken (NJ), USA: Wiley Interscience; pp. 1197–202. doi:10.1002/0471435139.tox060

Tsukioka T, Murakami T (1987). Capillary gas chromatographic-mass spectrometric determination of pyridine bases in environmental samples. *J Chromatogr A*, 396:319–26. doi:10.1016/S0021-9673(01)94069-5 PMID:3624377

Vainiotalo S, Väänänen V, Vaaranrinta R (2008). Measurement of 16 volatile organic compounds in restaurant air contaminated with environmental tobacco smoke. *Environ Res*, 108(3):280–8. doi:10.1016/j.envres.2008.07.020 PMID:18801480