

3-Picoline
[108-99-6]

Review of Toxicological Literature

Prepared for

Errol Zeiger, Ph.D.
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709
Contract No. N01-ES-65402

Submitted by

Raymond Tice, Ph.D. (Principal Investigator)
Brigette Brevard, M.A. (Co-Principal Investigator)
Integrated Laboratory Systems
P.O. Box 13501
Research Triangle Park, North Carolina 27709

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EXECUTIVE SUMMARY

3-Picoline (3-methylpyridine) was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing based on its high U.S. production volume and potential for human exposure. It is a colorless, volatile liquid with a sweet, pleasant odor, used as a solvent in the synthesis of pharmaceuticals, resins, dyes, rubber accelerators, as a laboratory reagent, and as an intermediate in the manufacture of insecticides, waterproofing agents, niacin, and niacinamide. It is produced from the vapor-phase reaction of acetaldehyde and ammonia with formaldehyde and/or methanol in the presence of a catalyst, from the reaction of acrolein with ammonia in the presence of acid catalyst, or from the pyrolysis of coal tar or bone oil. Its annual U.S. production volume is ~21.2-29.1 million lb (9.6-13.2 million kg).

3-Picoline may be determined in air or aqueous samples by means of gas chromatography (GC), high performance liquid chromatography (HPLC), or capillary zone electrophoresis (CZE).

3-Picoline biodegrades rapidly under aerobic conditions, and slowly under anaerobic conditions. It has an estimated half-life of 4.7 days (river model) to 37 days (lake model). Once volatilized, it exists in the vapor phase with an estimated half-life of 14.6 days. It has been detected in the ground water around wood-preserving facilities; in wastewater from shale oil processing plants; energy-processing plants, and coal gasification plants, and in surface oil-shale condensate retort water. 3-Picoline has been identified as a drinking water contaminant, a volatile component of boiled beef and mutton, and as a component of cigarette smoke.

3-Picoline is regulated by the United States Coast Guard (USCG), the U.S. Department of Transportation (DOT), and the U.S. Environmental Protection Agency (EPA).

Exposure to 3-picoline can occur in the workplace via dermal contact or inhalation. The general public can be exposed via contaminated drinking water or cigarette smoke.

3-Picoline is metabolized to 3-methylpyridine *N*-oxide in mice, rats, hamsters, guinea pigs, and rabbits. The oral LD₅₀ in mice and rats is 800-1600 mg/kg (8.59-17.18 mmol/kg) and 710 mg/kg (7.62 mmol/kg), respectively. The dermal LD₅₀ in rabbits is 126-200 mg/kg (1.35-2.15 mmol/kg) and in guinea pigs is 1000 mg/kg (10.74 mmol/kg). The inhalation LC₅₀ in rats is 3300 ppm (12.57 g/m³; 0.1350 mmol/m³). Rats exposed orally to 3-picoline showed reduced appetite and activity, weakness, acute gastrointestinal inflammation, hemorrhagic lungs, and liver discoloration. Rats exposed by inhalation died within 5 hours; autopsy revealed slight liver discoloration. In rabbits, dermal exposure to 3-picoline caused reduced appetite and activity, weakness, collapse, and

death; gastrointestinal irritation, hemorrhagic lungs, and slight liver discoloration were noted at autopsy. It is also a moderate to severe dermal and ocular irritant in rabbits.

In a subchronic inhalation study, male rats exposed to 3-picoline for 6 hours/day, 5 days/week for 2 weeks and sacrificed on day 10 had increased liver weights; while liver weights were normal in animals sacrificed on day 13. Rats fed a diet containing 10,000 mg/kg (107.38 mmol/kg) for 28 days exhibited slight growth inhibition and fatty liver.

In rats, 3-picoline induced a statistically significant increase in the length of time between pentylenetetrazole (PTZ)-induced myoclonic seizures, and decreased the severity of the seizures when compared to controls. In adult hens it partially inhibited tri-*o*-cresyl phosphate-induced ataxia.

3-Picoline was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without S9 metabolic activation.

No data on immunotoxicity, reproductive, teratological, or carcinogenic effects were located.

3-Picoline stimulated glutathione transferase (GST) activity in human liver-derived Hep G2 cells; the increase occurred via stimulation of the A1 subunit of GST. In another study, 3-picoline inhibited the diethylnitrosamine-induced ornithine decarboxylase (ODC) activity by 98% when co-administered intraperitoneally (i.p.) in male Wistar rats, indicating a relationship between ODC induction and nicotinamide adenine dinucleotide (NAD) metabolism. When combined with boiled pork juice condensate, 3-picoline induced a 52% increase in the number of mutant colonies of *S. typhimurium* strain TA98 (with induced rat liver S9) over the number of revertants induced by boiled pork juice alone.

Several studies investigated the relationship between the structure and biodegradability of pyridine derivatives, such as 3-picoline, and found that among pyridine compounds, the location and size of substituents on the pyridine ring affect biodegradation rates. 3-Picoline takes longer to biodegrade than monohydroxypyridines and the unsubstituted pyridine.

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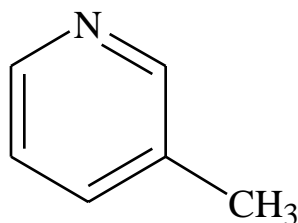
1.0 BASIS FOR NOMINATION

3-Picoline was nominated by the National Institute of Environmental Health Sciences (NIEHS) for toxicity and carcinogenicity testing based on its high U.S. production volume and potential for human exposure.

2.0 INTRODUCTION

3-Picoline

[108-99-6]



2.1 Chemical Identification

3-Picoline (C₆H₇N; mol. wt. = 93.128) is also called:

- Picoline
- 3-Methylpyridine
- Methylpyridine

(Budavari, 1996; ChemFinder, 1998)

2.2 Physical-Chemical Properties

Property	Information	Reference
Physical State	colorless liquid, hygroscopic	Budavari (1996)
Odor	sweet	Budavari (1996)
Boiling Point (°C)	143-144	Budavari (1996)
Melting Point (°C)	-18.3	Lewis (1993)
Density (g/mL)	0.957	Radian Corporation (1991)
Specific Gravity (@ 15 °C/4 °C)	0.9613	Budavari (1996)
Refractive Index (@ 24 °C)	1.5043	Budavari (1996)
Vapor Pressure (mm Hg @ 25 °C)	6.05	HSDB (1998)
Dissociation Constant (pKa @ 25 °C)	5.63-5.68	HSDB (1998)
Octanol-Water Partition Coefficient (log K _{ow})	1.20	HSDB (1998)
Water Solubility (20 °C, g/100 mL)	Miscible	Budavari (1996)
Other Solubilities	Very soluble in acetone; soluble in alcohol and ether	Lewis (1993); Budavari (1996)

2.3 Commercial Availability

3-Picoline is produced by Nepera, Inc. (Harriman, NY) and Reilly Industries (Indianapolis, IN) (SRI, 1997).

3.0 PRODUCTION PROCESSES AND ANALYSES

3-Picoline is produced from the vapor-phase reaction of acetaldehyde and ammonia with formaldehyde and/or methanol in the presence of a catalyst, or from the vapor-phase reaction of acrolein with ammonia in the presence of an acid catalyst (HSDB, 1998). It can also be produced using cyclohexamine plus ammonia and zinc chloride, or from the pyrolysis of coal tar or bone oil (Lewis, 1993).

3-Picoline has been analyzed by high performance liquid chromatography (HPLC) with ultraviolet (UV) detection and a reversed-phase column (limit of detection (LOD) n.p.) (McCalley, 1994), and capillary zone electrophoresis with UV detection (LOD n.p.) (Tanaka et al., 1995).

3-Picoline has been detected in water and sediment using gas chromatography (GC) with an LOD of 0.001 mg/L (0.011 µM) in water and 0.01 mg/L (0.11 µM) in sediment (HSDB, 1998). In air samples, it can be detected by charcoal absorption, followed by methylene chloride extraction, and subsequent GC analysis, with an estimated LOD of 7.59-30.4 mg/m³ (81.5-326

$\mu\text{mol}/\text{m}^3$; 1.99-7.98 ppm).

4.0 PRODUCTION AND IMPORT VOLUMES

3-Picoline is included on the U.S. Environmental Protection Agency's (EPA) High Production Volume Chemicals list with an annual U.S. production volume of ~21.2-29.1 million lb (9.6-13.2 million kg) (USEPA, 1998)

5.0 USES

3-Picoline is used as a solvent in the synthesis of pharmaceuticals (Jain et al., 1989), resins, dyes, and rubber accelerators, and as a laboratory reagent (Lewis, 1993). It is also used as an intermediate in the manufacture of insecticides, waterproofing agents, niacin, and niacinamide (Budavari, 1996).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

3-Picoline may be released into the environment via effluents from the manufacture and use of coal-derived liquid fuels and from the disposal of coal liquefaction and gasoline waste by-products (HSDB, 1998). Its use as a solvent, chemical intermediate, and laboratory agent may also result in its release in wastewater. It has an anticipated half-life of 4.7 days (river model) to 37 days (lake model). 3-Picoline is highly mobile in soil; the cation form may adsorb into clay and other soil material under acidic conditions. It is not expected to adsorb to suspended soil or sediment due to its high water solubility and low octanol-water partition coefficient. In the atmosphere, 3-picoline exists in the vapor phase with an estimated half-life of 14.6 days. Bioconcentration is not anticipated to be significant due to the low octanol-water partition coefficient and rapid biodegradation.

3-Picoline biodegrades rapidly under aerobic conditions and slowly under anaerobic conditions (Kuhn and Suflita, 1989). Results of a study of the bioorganic degradation of 3-picoline in rivers indicate that it is subject to biological attack by microorganisms present in surface water (Ettinger et al., 1954). Kaiser et al. (1993) studied the microbial transformation of 3-picoline under sulfate-reducing conditions in microbes isolated from a subsurface soil

previously exposed to *N*-substituted aromatic compounds for several years. In the presence of sulfate, 3-picoline was transformed to carbon dioxide and ammonia within 30 days. Benzoic acid was identified as a potential breakdown product.

3-Picoline has been identified as a contaminant in drinking water and in the ground water from two wood-preserving facilities in Pensacola, FL, at concentrations of 0.01-1.23 mg/L (0.11-13.2 μ M) (Hawthorne and Sievers, 1984). It was detected in the wastewater effluents of a wood-preserving facility at a concentration of 0.0007 mg/L (0.0075 μ M) and in 2 of 6 wastewater effluent samples from an energy-processing plant (concentration n.p.) (HSDB, 1998). It was also detected in wastewater from a coal gasification facility in Gillette, Wyoming, at a concentration of 6.2 mg/L (67 μ M). 3-Picoline has been identified as a volatile component of boiled beef and mutton, and as a component of cigarette smoke at concentrations of 12-36 μ g (0.13-0.39 μ mol) per cigarette (Hawthorne and Sievers, 1984).

7.0 HUMAN EXPOSURE

Occupational exposure to 3-picoline can occur dermally or via inhalation (HSDB, 1998). A study at a shale-oil facility found that 3-picoline was emitted to the air from wastewater. Non-occupational exposures can occur via contaminated drinking water and cigarette smoke. Higher air concentrations of 3-picoline were detected in the homes of smokers compared to non-smokers (HSDB, 1998).

8.0 REGULATORY STATUS

U. S. government regulations pertaining to 3-picoline are summarized in **Table 1**.

Table 1. Regulations Relevant to 3-Picoline

	Regulation	Summary of Regulation
E P A	40 CFR 60.489	3-Picoline is a volatile organic compound (VOC) regulated under performance standards for equipment leaks of VOCs by the Synthetic Organic Chemical Manufacturing Industry (SOCMI), which requires all newly constructed, modified, or reconstructed SOCMI units to demonstrate continuous emission reduction for equipment leaks.

Table 1. Regulations Relevant to 3-Picoline (Continued)

	Regulation	Summary of Regulation
	40 CFR 63.100 Subpart F	Under Section 112 of the Clean Air Act (CAA), as part of the national emission standards for organic hazardous air pollutants (59 FR 19454, Apr. 22, 1994), the EPA issued an order requiring all existing facilities that manufacture or use 3-picoline in their manufacturing process to comply with new air emission standards by January 23, 1995 (49 CFR 63.100). The newer standards are devised to reduce air emissions from chemical facilities by upgrading the manufacturing process.
E P A	40 CFR 716.120	3-Picoline is regulated under Section 8(d) of the Toxic Substances Control Act (TSCA), requiring manufacturers, importers, and processors to submit copies and lists of unpublished health and safety studies to the EPA.
	40 CFR 721.8775 Subpart B	The EPA regulates 3-picoline as a substituted pyridine and any significant new use is to be reported to the EPA under the authority of 5(a)(2) of TSCA. Section 8775 lists criteria for protective equipment, disposal, release to water, and chemical hazard program when working with 3-picoline.
U S C G	46 CFR 150.170	3-Picoline is considered a hazardous chemical when transported on an ocean going vessel. It is classified by the U.S. Coast Guard (USCG) as an aromatic amine (Cargo Group #9) and should be transported with other aromatic amines to avoid incompatibility or reactivity with other chemicals.
D O T	49 CFR 171-177	3-Picoline is classified as a hazardous material for transportation purposes. No person may transport, offer, or accept a hazardous material for transportation in commerce unless that person is registered in conformance with and the hazardous material is properly classed, described, packaged, marked, labeled, and in condition for shipment in accordance with hazardous materials regulations.
	49 CFR 172.101 Subpart B	3-Picoline is regulated by the U.S. Department of Transportation (DOT) when transported on land, water, or in the air. The following criteria apply: Shipping name: Picolines Hazard Classification: Flammable and combustible liquid Shipping Identification Number: UN2313 Packing Group: III (based on a flash point of 36°C) Packaging Labeled: Flammable Liquid Bulk Packaging Requirements: 49 CFR 173.242 Intermodal (IM) Tank Requirements: 49 CFR 173.102(c)(7)(i) Quantity Limit (per package): 60 L (Passenger Aircraft); 220 L (Cargo Aircraft)

9.0 TOXICOLOGICAL DATA

9.1 General Toxicology

9.1.1 Human Data

No human toxicity data were located.

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

3-Picoline given i.p. was metabolized to 3-methylpyridine *N*-oxide in mice, rats, hamsters, guinea pigs, and rabbits (Gorrod and Damani, 1980). Less than 7% of an i.p. dose (n.p.) of 3-picoline was excreted as 3-methylpyridine *N*-oxide in the urine of each species.

9.1.3 Acute Exposure

Acute toxicity values are presented in **Table 2**. The details of these studies are presented in **Table 3**.

Table 2. Acute Toxicity Values for 3-Picoline

Route	Species (sex and strain)	LD ₅₀ /LC ₅₀	Reference
Dermal	New Zealand albino rabbit, M	LD ₅₀ = 126-200 mg/kg (1.35-2.15 mmol/kg)	Monsanto Company (1972)
	guinea pig (sex and strain n.p.)	LD ₅₀ = 1000 mg/kg (10.74 mmol/kg)	RTECS (1998)
Inhalation	CrI:CD (SD)BR rat, M	LC ₅₀ = 3300 ppm (12.57 g/m ³ ; 0.1350 mol/m ³)	E. I. DuPont (1984a)
i.p.	mouse (sex and strain n.p.)	LD ₅₀ = 400-800 mg/kg (4.30-8.59 mmol/kg)	Eastman Kodak Company (1980)
	mouse (sex and strain n.p.)	LD ₅₀ = 596 mg/kg (6.40 mmol/kg)	Larson et al. (1946)
	rat (sex and strain n.p.)	LD ₅₀ = 100-200 mg/kg (1.07-2.15 mmol/kg)	Eastman Kodak Company (1980)
	Long-Evans hooded rat, M	7-day LD ₅₀ = 150 mg/kg (1.61 mmol/kg)	Dyer et al. (1985)
i.v.	mouse (sex and strain n.p.)	LD ₅₀ = 298 mg/kg (3.20 mmol/kg)	Larson et al. (1946)
Oral	mouse (sex and strain n.p.)	LD ₅₀ = 800-1600 mg/kg (8.59-17.18 mmol/kg)	Eastman Kodak Company (1980)
	Sprague-Dawley rat, M and F	LD ₅₀ = 710 mg/kg (7.62 mmol/kg)	Monsanto Company (1972)
	rat (sex and strain n.p.)	LD ₅₀ = 400-800 mg/kg (4.30-8.59 mmol/kg)	Eastman Kodak Company (1980)
	coturnix quail, red-winged blackbird, and starling (sexes n.p.)	LD ₅₀ = 1000 mg/kg (10.74 mmol/kg)	Schafer et al. (1983)

Abbreviations: n.p. = not provided; F = female; M = male; LC₅₀ = concentration lethal to 50% of test animals; LD₅₀ = dose lethal to 50% of test animals; i.p. = intraperitoneal injection; i.v. = intravenous injection.

Within 3 days, male and female Sprague-Dawley rats exposed orally to 710 mg/kg (7.62 mmol/kg) 3-picoline showed reduced appetite and activity, a bloody discharge from the eyes, and weakness (Monsanto Company, 1972). Pathologic findings included hemorrhagic lungs, liver discoloration, and acute gastrointestinal inflammation. Six of 6 male Sprague-Dawley rats exhibited signs of somnolence, muscle weakness, and shortness of breath and died within 5 hours when exposed by inhalation to 3100 ppm (11.81 g/m³; 126.8 mmol/m³); hemorrhagic lungs and

slight liver discoloration were noted at autopsy (Monsanto Company, 1972). All of 6 male Crl:CD (SD)BR rats died following exposure to 3300 ppm (12.57 g/m³; 135.0 mmol/m³) 3-picoline by inhalation for 4 hours (E. I. DuPont, 1984a). In another inhalation study (details n.p.), three of 3 rats died when exposed to 8700 ppm (33.14 g/m³; 355.9 mmol/m³) for 2 hours (Reinhardt and Brittelli, 1981). Treatment of fourteen male Long-Evans hooded rats with 100-200 mg/kg (1.07-2.15 mmol/kg) 3-picoline i.p. induced lethargy within minutes, which continued over the next several hours and ultimately resulted in the death of 1 of 5 rats in the 125 mg/kg (1.34 mmol/kg) group, 7 of 9 rats in the 175 mg/kg (1.88 mmol/kg) group, and 4 of 9 rats in the 200 mg/kg group (Dyer et al., 1985). Death occurred within 24-48 hours after treatment. 3-Picoline (100 mg/kg; 1.07 mmol/kg) administered i.p. induced mild, yet statistically significant (p<0.05) hypothermia compared to saline-treated controls (Dyer et al., 1985).

Following dermal (occluded) exposure to 79.4-2000 mg/kg (0.853-21.48 mmol/kg), male and female rabbits showed reduced appetite and activity, increasing weakness, collapse, and death, with hemorrhagic lungs, slight liver discoloration, and gastrointestinal irritation noted at autopsy (Monsanto Company, 1972). 3-Picoline was severely irritating to the eyes and skin of rabbits exposed dermally to 0.2 mL (0.2 g; 2 mmol) and ocularly to 0.1 mL (0.1 g; 1 mmol) for 24 hours. In another study, 3-picoline was classified as corrosive following a 4-hour dermal administration (occluded) of 0.5 mL (0.5 g; 5 mmol) to a one-inch square clipped area of the skin of 6 New Zealand albino rabbits (Costello, 1983). The area was examined and washed after 4 hours. Observations included slight to severe erythema, moderate edema, and corrosivity after 24 and 48 hours. In a separate study, male albino rabbits experienced moderate to severe dermal and ocular irritation following exposure to 3-picoline (doses n.p.) which was corrosive to the skin (Dutertre-Catella et al., 1989).

Table 3. Acute Exposure to 3-Picoline

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
<i>Rats</i>						
Sprague-Dawley, age n.p.	10 M, 10 F (5 animals/dose)	3-picoline, purity n.p.	oral: 501, 631, 794, and 1000 mg/kg (5.38, 6.78, 8.53, and 10.74 mmol/kg)	exposure and observation period n.p.	The survival time was 1-4 d, with most deaths occurring within 3 d. Toxic signs included reduced appetite and activity, ocular bloody discharge, increasing weakness, collapse, and death. Pathologic findings included hemorrhagic lungs, liver discoloration, and acute gastrointestinal inflammation.	Monsanto Company (1972)
	6 M		inhalation: 11.82 g/m ³ (126.9 mmol/m ³ ; 3103 ppm)	5-h exposure, observation period n.p.		
CrI:CD (SD) BR, 8 wk	6 M/dose	3-picoline, 98.5% pure	inhalation: 1300 ppm (4952 mg/m ³ ; 53.17 mmol/m ³) and 3300 ppm (12.57 g/m ³ ; 135.0 mmol/m ³)	4-h exposure, 14-d observation period	During exposure, rats in both groups were unresponsive. Following the 1300 ppm exposure, rats were limp and prostrate, with no righting reflex, and 1/6 had a red ocular discharge. Animals had severe weight loss for 1-2 d, followed by normal weight gain, and some had dry, red nasal and ocular discharges, wet perineum, decreased muscle tone, hypothermia, and paralysis. All effects disappeared 4 days post-exposure. All animals in the 3300 ppm exposure group died during the exposure. Rats had clear-to-red nasal discharge and labored breathing prior to death.	E. I. DuPont (1984a)
Rats, strain and age n.p.	3, sex n.p.	3-picoline, purity n.p.	inhalation: 8700 ppm (33.14 g/m ³ ; 355.9 mmol/m ³)	2-h exposure, observation period n.p.	Three of 3 rats died.	Reinhardt and Brittelli (1981)

Table 3. Acute Exposure to 3-Picoline (Continued)

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
Adult Long-Evans hooded, age n.p.	5 M low dose, 9 M each for mid and high doses; 14 M controls	3-picoline, 99% pure	i.p.: 125-200 mg/kg (1.34-2.15 mmol/kg)	single injection, 7-d observation period	The onset of effects was rapid, with animals becoming increasingly quiescent within minutes, and remaining so for several hours. Death occurred within 24-48 hours after administration of each dose in 1 of 5 rats (125 mg/kg group), 7 of 9 rats (175 mg/kg group), and 4 of 9 rats (200 mg/kg group),.	Dyer et al. (1985)
	6 M treated, 6 M controls		i.p.: 100 mg/kg (1.07 mmol/kg)		Mild, but statistically significant hypothermia was observed (rectal temperature measured at 15, 30, 60, 120, and 360 min).	
Rabbits						
New Zealand albino, age n.p.	4 M, 3 F	3-picoline, purity n.p.	dermal (occluded): 79.4, 126, 200, 316, 501, 1000, and 2000 mg/kg (0.853, 1.35, 2.15, 3.39, 5.38, 10.74, and 21.48 mmol/kg)	24-h exposure, 14-d observation period	Toxic signs included reduced appetite and activity (1-3 d in survivors), increasing weakness, collapse, and death. Necropsy revealed hemorrhagic lungs, slight liver discoloration, and gastrointestinal irritation. Each animal in the 4 highest doses died within 1 to 6 d.	Monsanto Company (1972)
	2 M, 1 F		dermal (occluded): 0.2 mL (0.2 g; 2 mmol)	24-h exposure, 7-d observation period	3-Picoline was severely irritating to the skin, causing flaking within 10-14 d. Effects included slight erythema and moderate edema after 24 h which improved after 72 h.	
	2 F, 1 M		ocular: 0.1 mL (0.1 g; 1 mmol)	24-h exposure, 10-d observation period	3-Picoline was severely irritating to the eyes. Animals showed signs of discomfort with moderate pawing, slight corneal dullness, moderate erythema, slight edema, and discharge after 10 min, a film over the cornea, and severe reduction or loss of pupillary reflex.	

Table 3. Acute Exposure to 3-Picoline (Continued)

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
New Zealand albino, age n.p.	6 M	3-picoline, purity n.p.	dermal (occluded): 0.5 mL (0.5 g; 5 mmol)	4 h exposure, followed by wash-off, 24-48 h observation period	Symptoms of severe erythema, moderate edema, and corrosivity were seen. 24-48 h after removal and washing off of the dose, mild-to-severe erythema was observed, with corrosivity remaining in 4 of 6 animals, and no edema noted in any animals. 3-Picoline was classified as corrosive.	Costello (1983)
New Zealand albino, age n.p.	6 M	3-picoline, >99% pure	dermal and ocular: doses n.p.	single exposure, animals sacrificed after 7 and 14 d	3-Picoline was irritating to the eyes, with histopathological findings of keratitis, lesions in corneal epithelial tissue, fibrillary edematous lamellae dissociation, and cellular inflammatory infiltration. It was severely irritating to the skin, with histopathological evidence of necrosis, ulceration, and regeneration.	Dutertre-Catella et al. (1989)

Abbreviations: n.p. = not provided; d = day(s); h = hour(s); M = male; F = female; i.p. = intraperitoneal injection; min = minute(s).

9.1.4 Short-Term and Subchronic Exposure

The details of these studies are presented in **Table 4**.

In a subchronic inhalation toxicity study of 10 male rats exposed to 290 ppm (1.10 g/m³; 11.8 mmol/m³) 3-picoline for 6 hours per day, 5 days per week for 2 weeks, necropsy revealed increased liver weights in animals sacrificed after 10 exposures; liver weights were normal in animals sacrificed 13 days post-exposure (E. I. DuPont, 1984b).

In a 28-day study (details n.p.), rats fed a diet containing 10,000 mg/kg (107.38 mmol/kg) 3-picoline exhibited slight growth inhibition and an increased liver fat content (E. I. DuPont, 1992).

9.1.5 Chronic Exposure

No chronic exposure data were located.

9.1.6 Antitoxicity of 3-Picoline

The details of these studies are presented in **Table 5**.

In rats, 3-picoline (100 mg/kg; 1.07 mmol/kg) induced a statistically significant increase in the length of time between pentylenetetrazole (PTZ)-induced myoclonic seizures. The severity of the seizures was decreased, although not significantly, compared to controls (Dyer et al., 1985).

3-Picoline (0.5-1 mmol/kg; 0.05-0.09 g/kg) partially inhibited tri-*o*-cresyl phosphate-induced ataxia in adult hens (Chambers and Casida, 1967).

9.2 Reproductive and Teratological Effects

No reproductive or teratological data were located.

9.3 Carcinogenicity

No carcinogenicity data were located.

Table 4. Short-Term and Subchronic Exposure to 3-Picoline

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
CrI:CD (SD)BR rats, 8 wk	10 M treated, 10 M controls	3-picoline, 98.5 % pure	inhalation: 290 ppm (1.10 g/m ³ ; 11.8 mmol/m ³)	exposed 6 h/d, 5 d/wk for 2 wk, 13-d observation period	Necropsy revealed increased liver weights after 10 exposures; liver weights were normal after 13 d.	E. I. DuPont (1984b)
Rats, strain and age n.p.	Number and sex n.p.	3-picoline, purity n.p.	oral: 10,000 mg/kg (107.38 mmol/kg)	28-d exposure, observation period n.p.	Slight growth inhibition and an increased liver fat content.	E. I. DuPont (1992)

Abbreviations: n.p. = not provided; M = male; d = day(s); wk = week(s); h = hour(s).

Table 5. Antitoxicity of 3-Picoline

Species Strain, and Age	Number and Sex of Animals	Chemical Form and Purity	Route/Dose	Exposure/Observation Period	Results/Comments	Reference
Adult Long-Evans hooded rats, age n.p.	24 M treated, 24 M control (actual number used in data analysis varied with each test due to technical problems)	3-picoline, 99% pure	i.p.: 100 mg/kg (1.07 mmol/kg)	Single injection, 45-min observation period	3-Picoline induced a statistically significant increase in the length of time between PTZ-induced myoclonic seizures, the severity of the seizures was decreased but not significantly.	Dyer et al. (1985)
Adult hens (strain and age n.p.)	5 to 15, sex n.p.	3-picoline, purity n.p.	i.p.: 0.05-0.09 g/kg (0.5-1 mmol/kg)	10-d exposure, 15-d observation period	3-Picoline partially inhibited tri- <i>o</i> -cresyl phosphate-induced ataxia in adult hens.	Chambers and Casida (1967)

Abbreviations: n.p. = not provided; d = day(s); M = male; i.p. = intraperitoneal injection; min = minute(s); PTZ = pentylenetetrazole.

9.4 Genotoxicity

The details of these studies are presented in **Table 6**.

3-Picoline was tested for mutagenicity in the *Salmonella typhimurium* assay; all tests gave negative results. 3-Picoline (0.01-1.00 mg/plate; 0.11–10.7 $\mu\text{mol}/\text{plate}$) was not mutagenic in the *S. typhimurium* plate incorporation assay with strain TA98 in the presence of Aroclor-induced rat liver S9 metabolic activation enzymes (Ho et al., 1981). Haworth et al. (1983) reported negative results with 3-picoline (85.4-8540 $\mu\text{g}/\text{plate}$; 0.917-91.70 $\mu\text{mol}/\text{plate}$) in a preincubation assay with *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without Aroclor-induced rat or hamster liver S9. Negative results were also obtained in investigations of the mutagenic activity of 3-picoline in the *S. typhimurium* plate incorporation assay with strains TA97, TA98, TA100, and TA102, with and without induced rat liver S9 (Claxton et al., 1987; Lee et al., 1994).

9.5 Immunotoxicity

No immunotoxicity data were located.

9.6 Other Data

9.6.1 Effect on Glutathione Transferase Activity

3-Picoline (5 mM; 0.5 mg/mL) stimulated glutathione transferase (GST) activity in human liver-derived Hep G2 cells (Dierickx, 1994). The increases in GST activity occurred via stimulation of the A1 subunit of GST.

9.6.2 Inhibition of Ornithine Decarboxylase Activity

3-Picoline (3.75 mmol; 349 mg) inhibited the induction of ornithine decarboxylase (ODC) activity by diethylnitrosamine (DEN) (200 mg/kg; 2.15 mmol/kg) by 98% when co-administered i.p. to male Wistar rats (Sakamoto et al., 1987). Agents that inhibit DEN-induced ODC activity in the liver, such as 3-picoline, are metabolized to niacin in the liver and are precursors to nicotinamide adenine dinucleotide (Weiner and van Eys, 1983; cited by Sakamoto et al., 1987).

Table 6. Genotoxicity of 3-Picoline

Test System	Biological Endpoint	+/- S9	Chemical Form, Purity	Dose	Endpoint Response	Reference
<i>Salmonella typhimurium</i> strain TA98	<i>his</i> gene mutations	+	3-picoline, purity n.p.	0.01-1.00 mg/plate (0.11-10.7 µmol/plate)	Negative	Ho et al. (1981)
<i>S. typhimurium</i> strains TA100, TA1535, TA1537, and TA98	<i>his</i> gene mutations	+/-	3-picoline, 98% pure	85.4-8540 µg/plate (0.917-91.70 µmol/plate)	Negative	Haworth et al. (1983)
<i>S. typhimurium</i> strains T97, TA98, TA100, and TA102	<i>his</i> gene mutations	+/-	3-picoline, 99.0% pure	10-5000 µg/plate (0.11-53.69 µmol/plate)	Negative	Claxton et al. (1987)
<i>S. typhimurium</i> strains TA100, TA98	<i>his</i> gene mutations	+/-	3-picoline, purity n.p.	n.p. (believed to be up to 100 µmol/plate, based on data presented from 6 other compounds tested)	Negative – data not shown	Lee et al. (1994)

Abbreviations: n.p. = not provided; “+” = positive; “-” = negative.

9.6.3 Modulation of Genotoxicity

When combined with boiled pork juice condensate in a *S. typhimurium* plate incorporation assay, 3-picoline induced a 52% increase in the number of mutant colonies of strain TA98 (with induced rat liver S9) over the number of revertants induced by boiled pork juice alone (Lee et al., 1995).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Environmental Biodegradation

In a biodegradation study using aerated plant waste, Miller and Boyle (1976) concluded that among pyridine bases, pyridine is most readily digested by biodegrading microorganisms, followed by picolines, with lower alkylpyridines favored least by the bacteria. The location and size of substituents on the compounds affect the rate of biodegradation.

Rodgers et al. (1985) found differences in the rates of the microbiological degradation of a mixture of alkylpyridines in groundwater maintained under aerobic and anaerobic conditions. The presence of alkyl substituents on the pyridine ring affected biodegradation rates under aerobic conditions, but had no effect on anaerobic degradation rates.

Sims and Sommers (1986) examined the relationship between structure and biodegradability of pyridine derivatives under anaerobic conditions. The authors found that pyridinecarboxylic acids, monohydroxypyridines, and the unsubstituted pyridine ring did not volatilize and were completely degraded within 7-24 days; however, methylpyridines, including 3-picoline, were extensively volatilized and took more than 30 days to biodegrade. Of the chloropyridines, only 4-chloropyridine was completely degraded within 24 hours, and was extensively volatilized.

Mutagenicity

Claxton et al. (1987) examined the potential mutagenicity and structure-activity of 16 pyridine derivatives in the Salmonella assay with and without metabolic activation. The authors found that the halogenated pyridines, particularly those with halogens at the 2-position, and

singly on a methyl substituent, have mutagenic activity. Non-halogenated methyl analogues, such as 3-picoline, were not mutagenic.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)

TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

Chemical Economics Handbook (CEH)

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS

EMBASE

Registry

CANCERLIT

HSDB

RTECS

CAPLUS

MEDLINE

TOXLINE

CHEMLIST

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSH TIC	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB

Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Developmental and Reproductive Toxicology	DART

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Radian Corporation. 1991. Beta-Picoline. National Toxicology Program (NTP) Chemical Repository. http://ntp-db.niehs.nih.gov/NTP-Reports/NTP_Chemc_S&S/NTP_Chem1/Radian108-99-6.txt (12/1/98)

In-House Databases

CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette
The Merck Index, 1996, on CD-ROM

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APPENDIX A UNITS AND ABBREVIATIONS

°C = degrees Celsius

µg = micrograms

µg/L = micrograms per liter

µg/m³ = micrograms per cubic meter

µg/mL = micrograms per milliliter

µM = micromolar

µmol/L = micromoles per liter

µmol/plate = micromoles per plate

µL = microliter

CAA = Clean Air Act

CFR = Code of Federal Regulations

d = day(s)

DOT = U. S. Department of Transportation

EPA = U. S. Environmental Protection Agency

F = female

g = grams

g/m³ = grams per cubic meter

g/mL = grams per milliliter

g/L = grams per liter

GC = gas chromatography

GI = gastrointestinal

GST = glutathione transferase

h = hour(s)

HPLC = high performance liquid chromatography

IM = intermodal

i.p. = intraperitoneal injection

i.v. = intravenous injection

kg = kilograms

kg/yr = kilograms per year

k_{ow} = octanol/water partition coefficient

lb = pounds

LC₅₀ = concentration lethal to 50% of test animals

LD₅₀ = dose lethal to 50% of test animals

LD_{LO} = minimum lethal concentration

M = male

mg = milligrams

mg/kg = milligrams per kilogram

mg/m³ = milligrams per cubic meter

mg/mL = milligrams per milliliter

mg/L = milligrams per liter

mg/plate = milligrams per plate

min = minute(s)

mL/kg = milliliters per kilogram

mm = millimeters

mm Hg = millimeters mercury

mM = millimolar

mmol = millimoles

mmol/kg = millimoles per kilogram

mmol/L = millimoles per liter

mo = month(s)

mol/m³ = moles per cubic meter

mol. wt. = molecular weight

NAD = nicotine adenine dinucleotide

nmol/L = nanomoles per liter

n.p. = not provided

NA = not applicable

ODC = ornithine decarboxylase

OPPT = Office of Pollution Prevention and Toxics

pKa = dissociation constant

ppb = parts per billion

ppm = parts per million

PTZ = pentylenetetrazole

s.c. = subcutaneous

SOCMI = Synthetic Organic Chemical Manufacturing Industry

TSCA = Toxic Substances Control Act

USCG = United States Coast Guard

UV = ultraviolet

VOC = volatile organic compound

wk = week(s)