SUMMARY OF DATA FOR CHEMICAL SELECTION

2-CHLOROPYRIDINE

CAS NO. 109-09-1

BASIS OF NOMINATION TO THE CSWG

2-Chloropyridine was one of a group of pyridine derivatives screened for mutagenicity and carcinogenicity data to identify candidate chemicals for genetic toxicity testing (Ames/*Salmonella* or mouse lymphoma assay) in the National Cancer Institute, Division of Cancer Biology's (NCI/DCB's) Short-Term Testing Program. Subsequently, it was reported in the chemical press that a major manufacturer of this chemical, Olin Corporation, was planning to double production capacity of this "key intermediate" at its Rochester, NY, plant. 2-Chloropyridine is presented to the CSWG as a candidate for nomination for testing by the National Toxicology Program (NTP) because of:

- increasing production and use as a pharmaceutical and agrochemical intermediate
- potential for occupational and environmental exposures
- evidence of mutagenicity based on results in several short-term test systems
- suspicion of carcinogenicity based on structure and evidence of mutagenic or carcinogenic effects associated with structurally related chemicals

SELECTION STATUS

ACTION BY CSWG: 12/3/96

Studies requested:

- Preliminary dermal studies in transgenic mouse

Priority: High

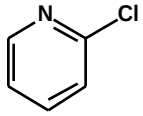
Rationale/Remarks:

- Potential for occupational exposure
- Positive mutagenicity data
- Suspicion of carcinogenicity
- Transgenic model to be selected by NTP

CHEMICAL IDENTIFICATION

CAS Registry Number:	109-09-1
Chemical Abstracts Service Name:	Pyridine, 2-chloro- (9CI); 2-chloropyridine (8CI)
Synonyms and Trade Names:	alpha-Chloropyridine; *o*-chloropyridine
Structural Class:	Halopyridine

Structure, Molecular Formula and Molecular Weight:



C_5H_4ClN Mol. wt.: 113.55

Chemical and Physical Properties:

Description:	Colorless, oily liquid (Sax & Lewis, 1987)
Boiling Point:	170%C (Sax & Lewis, 1987)
Solubility:	Solubility in water: 2.5 g/100g @ 25°C; soluble in alcohol and ether (Reilly Industries, Inc., 1990; Lide, 1995)
Density:	1.205 g/cm^3 @ 15°C (Lide, 1995)
Stability:	Slight fire hazard when exposed to heat or flame; evolves phosgene on heating to decomposition (Sax & Lewis, 1987; Gehring, 1983)
Log P:	1.22 or 1.34 @ pH 7 (Hansch *et al.*, 1995)

Technical Products and Impurities: 2-Chloropyridine is available as Æ99% pure product from Aldrich Chemical Co., Eastman Chemical Co., Fisher Scientific, Olin Corp., and Reilly Industries, Inc. In addition to the purified (99%) grade, Olin Corp. supplies this chemical in 55 gallon drum quantities in technical (95%) and crude (80%) grades (Aldrich Chemical Co., 1996; Eastman Chemical Co., 1993; Fisher Scientific, 1995; Kuney, 1994; Reilly Industries Inc., 1990).

EXPOSURE INFORMATION

Production and Producers: 2-Chloropyridine can be prepared by the direct chlorination of pyridine in the vapor phase at >300°C in the presence of a diluent; 2,6-dichloropyridine occurs as a by-product (Goe, 1982). Reilly Industries, Inc., has recently patented an improved process for 2-chloropyridine's manufacture based on this basic method. Reilly's synthesis involves the selective chlorination of

pyridine with Cl_2 in an inert gas (N_2) in the presence of water vapor and in two stages at elevated temperatures of Ç470º followed by Ç290º (Toomey, 1994). According to Gehring (1983) this chemical is prepared for use as a chemical intermediate by heating potassium pyrrole with chloroform. Two other patented processes for industrial manufacture of 2-chloropyridine are described as follows:

•Reaction of _-picoline with Cl_2 in the gas phase in the presence of H_2O and a catalyst, such as pyrophyllite, yielding a mix of chlorinated pyridines (Sharvit *et al.*, 1987).

•Reaction of 2-hydroxypyridine with phosgene in the presence of an amide, such as N,N-dimethylformamide (Tamura *et al.*, 1995).

2-Chloropyridine is listed in the EPA's TSCA Inventory (STN International, 1996a). The EPA received no reports of annual 1993 production of Æ10,000 lbs. by U.S. manufacturers, according to Walker (1996). Nevertheless, 2-chloropyridine is listed as a chemical in commerce in the U.S. International Trade Commission (USITC) publication, *Synthetic Organic Chemicals, US Production and Sales, 1993* (USITC, 1994). The reporting company was listed as Olin Corp.; but no production or sales quantities were included. According to the USITC, separate statistics were not published to avoid disclosure of individual company operations; however, the USITC reporting guidelines specify that each company's report of a chemical represents production of Æ4,500 kg [10,000 lbs] or sales Æ$10,000. A recent news article in the chemical press reported that Olin Corp. will double its capacity for 2-chloropyridine production at its Rochester, N.Y. facility in the next several years (Anon., 1996). According to recent issues of chemical catalogs and directories, 2-chloropyridine is manufactured and/or distributed not only by Olin Corp., but also by AC Industries Inc., Aceto Corp., Aldrich Chemical Co., Chugai Boyeki (America) Corp., Fabrichem, Inc., Maypro Industries, Inc., Reilly Industries, Inc. and WEYL GmbH/Ruetgers-Nease Corp. (Aldrich Chemical Co., 1996; Avocado Research Chemicals, Ltd., 1996; Eastman Chemical Co., 1993; Kuney, 1994; Hunter, 1995; Van, 1995).

Use Pattern: 2-Chloropyridine is used as an intermediate in synthetic organic, pharmaceutical and agricultural chemical (fungicides, herbicides) manufacture. It is also used as a catalyst for phase transfer (Lewis, 1993; Kuney, 1994). According to Olin Corp., it is a key intermediate in the manufacture of pyrithione-based biocides for use in cosmetics and various pharmaceutical products (Anon., 1996). 2-Chloropyridine is used as a starting material in the production of the antihistamine drug, pheniramine, and the antiarrhythmic, disopyramide (Goe, 1982).

Human Exposure: There is potential for occupational exposures to 2-chloropyridine during its production and use as an industrial chemical intermediate. An *Industrial Hygiene Survey* of the Olin Corp. Rochester, NY, plant noted that significant exposures to chemicals in the 2-chloropyridine

processing area existed, that high vapor concentrations resulting from liquid spills and also from minor leaks were detected in the rooms of the closed processing area of the 2-chloropyridine process, and that personnel should continue to be sampled quarterly for exposures (EPA, 1983). 2-Chloropyridine is not listed in the National Occupational Exposure Survey (NOES).

Gehring and coworkers (1967) noted that the solubility of 2-chloropyridine in organic solvents suggested that it might be readily absorbed when applied to the skin. Subsequently, Gehring (1983) reported that experimental evidence suggests that chlorinated pyridines are rapidly absorbed through intact skin.

Environmental Occurrence: 2-Chloropyridine has not been reported to occur naturally; however, it is reported to be an environmental contaminant. The Dow Chemical Co. has identified it as a trace organic chemical in process streams and wastewater (Melcher & Bouyoucos, 1990). It has also been identified as a Rhine River pollutant in the Netherlands and a trace organic contaminant in drinking water derived from river water in Barcelona, Spain (Hendricks *et al.*, 1994; Guardiola *et al.*, 1991).

2-Chloropyridine was detected as an intermediate product in amended freshwater sediment slurries; it arose from the biotransformation of 2,3-dichloropyridine under anaerobic (methanogenic) conditions. It was reported to be persistent and not to be further metabolized during the 6 month incubation period, according to Liu (1995). Adrian and Suflita (1994) also reported that 2-chloropyridine resisted biodegradation in anoxic aquifer slurries incubated for 11 months.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace maximum allowable levels of 2-chloropyridine. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a threshold limit value (TLV) or biological exposure index (BEI) for this compound. 2-Chloropyridine is classified as a poisonous material by the U.S. Department of Transportation and assigned DOT #2822 (Business & Legal Reports, Inc.. 1995).

The Environmental Protection Agency (EPA) has issued a TSCA Section 8(d) requirement for health and safety data reporting on pyridine and pyridine derivatives, including 2-chloropyridine (EPA, 1983).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: 2-Chloropyridine is reported to be irritating and toxic by ingestion (Lewis, 1993; Aldrich Chemical Co., Inc., 1996).

The pathology caused by exposure to 2-chloropyridine is essentially the same as that caused by exposure to pyridine. Exposures less than those required to produce overt clinical signs may cause varying degrees of liver damage with central lobular fatty degeneration, congestion, and cellular infiltration; repeated low-level exposures cause cirrhosis. The kidney is less sensitive to pyridine-induced damage than is the liver. In general, pyridine and its derivatives cause local irritation on contact with the skin, mucous membranes, and cornea (Gehring, 1983).

No epidemiological studies or case reports investigating the association of exposure to 2-chloropyridine and cancer risk in humans were identified in the available literature.

Animal Data: The acute toxicity of 2-chloropyridine has been studied in rats, mice and rabbits. Following single dose inhalation of 2-chloropyridine vapors in rats the liver was the primary target organ. Gross lesions included central lobular necrosis, hemorrhage, and fatty degeneration as well as cellular infiltration. Maximum exposures not causing these changes were 100 ppm for 3 minutes, 50 ppm for 6 minutes, 25 ppm for 12 minutes, and 10 ppm for 30 minutes. Maximum single-dose exposures that did not cause death were 1,000 ppm for 6 minutes, 500 ppm for 12 minutes, 250 ppm for 30 minutes, 100 ppm for 2 hours, and 50 ppm for 4 hours (Gehring *et al*., 1967).

In mice, 2-chloropyridine is somewhat more toxic when given orally than when given by intraperitoneal injection. The mouse oral LD_{50} is 110 mg/kg, and the intraperitoneal LD_{50} is 130 mg/kg. Gross lesions included swollen and fatty livers as well as hemorrhage and necrosis at higher doses and swollen, edematous kidneys in some animals. Concurrent administration of methionine but not cysteine or nicotinamide had a protective effect against the toxicity; both cysteine and nicotinamide augmented the toxicity (Gehring *et al.*, 1967).

In rabbits, 2-chloropyridine was essentially as toxic when applied to the skin as when given by intraperitoneal injection. The rabbit dermal LD_{50} is 48 mg/kg, and the intraperitoneal LD_{50} is 64 mg/kg. The primary gross lesion, regardless of route of administration, was hemorrhagic necrosis of the liver. Installation of undiluted or 10% 2-chloropyridine solution in propylene glycol in the eyes of rabbits caused severe inflammation of the conjunctiva and moderate clouding of the cornea that persisted for 48 hours (Gehring *et al.*, 1967).

No 2-year carcinogenicity studies of 2-chloropyridine in animals were identified in the available literature. 2-Chloropyridine is listed by the NTP in the name file only; no test data have been reported, nor are any tests planned or in progress (NTP, 1995).

Short-Term Tests: Claxton and coworkers (1987) reported that 2-chloropyridine was mutagenic when tested at concentrations up to 7500 _g/plate in the *Salmonella typhimurium*/ mammalian microsome assay in strains TA97, TA98, TA100 and TA102 with metabolic activation, but non-mutagenic when tested in the same strains at concentrations up to 5000 _g/plate without activation. Chlopkiewiz and coworkers (1993) designed a study in strain TA100 to explain the possible role of N-oxidation and ˙OH radicals in 2-chloropyridine mutagenesis. They found that the exclusive mutagenicity of 2-chloropyridine in the presence of metabolic activation was completely suppressed by preincubation for 10, 20, or 30 minutes with S9; partially or totally suppressed by glutathione and the ˙OH radical scavengers, mannitol and thiourea; and not suppressed by catalase, superoxide dismutase, or hydroquinone. Further, the mutagenicity of 2-chloropyridine in the presence of 2-chloropyridine N-oxide, a metabolite of 2-chloropyridine, was similar to that observed in the presence of glutathione or ˙OH radical scavengers. Pyridine N-oxide alone was not mutagenic. They noted that their results: (1) do not permit a conclusion regarding whether the mutagenicity of 2-chloropyridine was caused by ˙OH radicals, or whether other species generated intracellularly were involved; and (2) confirmed the assumption that N-oxidation of pyridines may protect the cells from the effects of reactive oxygen species.

Zimmermann and coworkers (1986) reported 2-chloropyridine to be one of a series of pyridine derivatives which induced mitotic aneuploidy in *Saccharomyces cerevisiae*.

In V_3 cells (an African Green monkey kidney cell line) incubated with 400 to 3,200 &g/ml of 2-chloropyridine, the incidence of chromosomal aberrations was similar to that in untreated controls. However, when tested in combination with 1,600 &g/ml pyridine N- oxide, 200 &g/ml 2-chloropyridine induced chromosomal aberrations in 25% of the cells compared with 5% in cells treated with pyridine N-oxide alone (Anuszewska & Koziorowska, 1995).

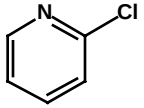
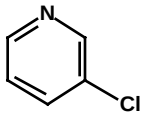
When tested in the L5178Y mouse lymphoma mammalian system, 2-chloropyridine, tested at concentrations up to 2004 &g/ml, induced gene mutations and structural chromosome aberrations with and without metabolic activation. In the presence of exogenous metabolic activation the positive response, which included induction of both small and large tk mutants, was greatly increased. 2-Chloropyridine also induced micronuclei with and without activation (Dearfield *et al.*, 1993).

Metabolism: When incubated with liver homogenate and cofactors, 2-chloropyridine yields 2-chloropyridine N-oxide and pyridine N-oxide (Chlopkiewicz *et al.*, 1993).

Structure Activity Relationships: Six compounds, structurally similar to 2-chloropyridine, were screened for relevant information associating these related chemicals with a mutagenic or carcinogenic effect. No information was found on the carcinogenicity or mutagenicity of 2-chloropyrimidine [1722-12-9], chloropyrazine [14508-49-7], or 2-bromopyridine [109-04-6]. Information on carcinogenicity was identified for two of the compounds, chlorobenzene and 2-chloroquinoline. Mutagenicity data were available on three of the compounds, 3-chloropyridine, chlorobenzene, and 2-chloroquinoline. A summary of information found in the available literature is presented in Table 1.

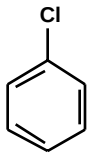
Dearfield and coworkers (1993) postulated that halogenated pyridine derivatives substituted directly at the 2-position exert genotoxic effects through N-oxidation by microsomal enzymes.

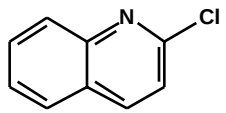
Table 1. Summary of Information on 2-Chloropyridine and Structurally Related Compounds

Chemical Name	Carcinogenicity Data	Mutagenicity Data	Other Data
2-Chloropyridine [109-09-1] 		positive in *S. typhimurium* strains TA97, TA98, TA100, and TA102 with but not without metabolic activation. However, mutagenicity was completely suppressed by preincubation for 10, 20, or 30 minutes with S9; partially or totally suppressed by glutathione, the OH^- scavengers, mannitol and thiourea, and 2-chloropyridine N-oxide; not suppressed by catalase, superoxide dismutase, or hydroquinone (Claxton *et al*., 1987; Chlopkiewicz *et al.*, 1993) induced mitotic aneuploidy in *S. cerevisiae* (Zimmerman *et al*., 1986) negative for chromosomal aberrations in V_3 cells when tested alone but positive in combination with pyridine N-oxide (Anuszewska & Koziorowska, 1995)	
3-Chloropyridine [626-60-8] 		negative in *S. typhimurium* strains TA98, TA100, TA97, and TA102 at doses up to 5,000 &g/plate with or without metabolic activation (Claxton *et al*., 1987) negative in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 at doses up to 5 mg/plate (Simmon *et al*., 1977) positive for chromosomal aberrations in V_3 cells; protective effect by pyridine N-oxide (Anuszewska & Koziorowska, 1995) positive for gene mutations and chromosomal aberrations with and without metabolic activation in mouse lymphoma cells (Dearfield *et al*., 1993) positive for micronuclei in mouse lymphoma cells (Dearfield *et al*., 1993)	

Prepared by Technical Resources International, Inc. under contract No. NO2-CB-50511 (10/96; rev. 8/97)

Table 1. Summary of Information on 2-Chloropyridine and Structurally Related Compounds (continued)

Chemical Name	Carcinogenicity Data	Mutagenicity Data	Other Data
3-Chloropyridine (continued)		positive for gene mutation and chromosomal aberration induction with and without metabolic activation; positive for micronuclei induction without but not with metabolic activation (Dearfield *et al*., 1993)	
Chlorobenzene [108-90-7] 	following oral administration (gavage) of 60 or 120 mg/kg, 5 days/week for 103 weeks in F344/N rats and $B6C3F_1$ mice, induced neoplastic nodules of the liver in male rats in the high dose group; no neoplastic changes observed in female rats and male and female mice (NTP, 1985) categorized by EPA as a class D carcinogen (inadequate evidence of carcinogenicity in humans and animals) based on the results of the NTP study (ATSDR, 1990)	negative in *in vitro* bacterial and yeast assay systems with and without metabolic activation including in *S. typhimurium* at doses up to 333.3 &g/plate (ATSDR, 1990; NTP, 1985) negative for DNA damage in *E. coli* (ATSDR, 1990) weakly positive in an *in vivo* mouse bone marrow chromosomal aberration assay (Shelby *et al.,* 1995) induced DNA damage in peripheral lymphocytes but not bone marrow cells from C57BL/6 female mice (Vaghef & Hellman, 1995) induced cell transformation in rat liver epithelial cells (ATSDR, 1990) moderately positive in an *in vivo* micronuclear test in mice (ATSDR, 1990) negative in an *in vivo* mouse bone marrow micronucleus test (Shelby *et al.,* 1995)	developmental effects (maternal toxicity but no structural malformations) in rats and rabbits following inhalation of vapors at concentrations up to 590 ppm during periods of major organogenesis (ATSDR, 1990) no reproductive effects in a 2-generation study in rats administered up to 450 ppm (ATSDR, 1990) no teratogenic effects in rats gavaged with 100 or 300 mg/kg from days 6-15 of gestation (ATSDR, 1990)
2-Chloroquinoline [612-62-4]	no tumors, hyperplastic changes, or other neoplastic changes in 15 (effective) rats fed	negative in *S. typhimurium* strains TA98 and TA100 with and without metabolic activation (Nagao *et al*., 1977; Sideropoulos & Specht, 1984; Kamiya *et al*., 1990)	

	0.25% in diet for 40 weeks (Hirao *et al.*, 1976)		

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