SUMMARY OF DATA FOR CHEMICAL SELECTION

2-ACETYLPYRIDINE
CAS NO. 1122-62-9

BASIS OF NOMINATION TO THE CSWG

2-Acetylpyridine 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. Very limited toxicological information was found on 2-acetylpyridine. This compound was subsequently identified in an article in the general consumer press as an aroma chemical being used experimentally in humans to suppress appetite and promote weight loss. 2-Acetylpyridine is presented to the CSWG as a candidate for nomination for testing by the National Toxicology Program (NTP) because of:

•potential for occupational or environmental exposures as a result of production or processing

•potential for general and consumer population exposures based on its natural occurrence as a flavor/aroma constituent and wide use as a component in processed food products and in aroma therapy

•lack of genetic and chronic toxicity test data

•suspicion of carcinogenicity based on pyridyl ketone structure.

SELECTION STATUS

ACTION BY CSWG: 7/16/97

Studies requested:

- *In vitro* cytogenetics
- Carcinogenicity

Priority: High for *in vitro* cytogenetics; moderate for carcinogenicity

Rationale/Remarks:

- Potential for general and consumer exposure based on its occurrence and uses
- Lack of genetic and chronic toxicity data
- Suspicion of carcinogenicity based on its structure

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

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2-Acetylpyridine
1122-62-9

Dr. Daniel Benz, Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), provided information on 2-acetylpyridine from FDA's Priority-Based Assessment of Food Additives (PAFA) database.

UPDATE OF MUTAGENICITY STUDIES

2-Acetylpyridine was presented at the December 1996 CSWG meeting and deferred pending results of the NCI Short-Term Test Program. The results are as follows: negative in the Ames *Salmonella typhimurium* assay with and without activation; weak positive response in the mouse lymphoma (ML) assay at the highest dose tested with activation; the ML test without activation is being repeated.

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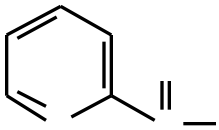
2-Acetylpyridine
1122-62-9

CHEMICAL IDENTIFICATION

CAS Registry Number:	1122-62-9
Chemical Abstracts Service Name:	Ethanone, 1-(2-pyridinyl)- (9CI); ketone, methyl 2-pyridyl (8CI)
Synonyms and Trade Names:	2-Acetylpyridine; -acetylpyridine; 2-acetopyridine; 2-pyridyl methyl ketone; methyl 2-pyridinyl ketone
Structural Class:	Pyridyl ketone

Structure, Molecular Formula and Molecular Weight:



C_7H_7NO Mol. wt.: 121.14

Chemical and Physical Properties:

Description:	Volatile liquid with heavy, oily, fatty, popcorn- like aroma (Aldrich Chemical Co., Inc., 1996a)
Boiling Point:	192.3%C (Reilly Industries Inc., 1990)
Freezing Point:	10.7%C (Reilly Industries Inc., 1990)
Density:	1.077 g/cm^3 @ 25%C (Lide, 1995)
Solubility: alcohol, ether,	Solubility in water: 18.2 g/100g @ 25^{o}C; soluble in and acetate; slightly soluble in carbon tetrachloride (Reilly Industries, Inc., 1990; Lide, 1995)
Volatility:	Aromatic volatile organic compound
Reactivity: reactions	Especially reactive in typical methyl ketone additions to the carbonyl and condensations at the methyl group (Goe, 1982)
Log P:	0.85 (Hansch *et al*., 1995)

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Technical Products and Impurities: 2-Acetylpyridine is available at a purity of 98 to >99% from Aldrich Chemical Co., Alfa *ÆSAR*, Fluka Chemical Corp., Lancaster Synthesis, Inc., and Reilly Industries, Inc. (Aldrich Chemical Co., 1996b; Avocado Research Chemicals, Ltd., 1996; Fluka Chemical Corp., 1995; Lancaster Synthesis, Inc., 1995; Reilly Industries, Inc., 1990).

EXPOSURE INFORMATION

Production and Producers: 2-Acetylpyridine can be prepared by the catalytic air oxidation of 2-ethylpyridine in the liquid phase (Goe, 1982). Two other preparative methods are described in the recent chemical literature as follows:

- Grignard reaction of 2-cyanopyridine with organolithium (CH_3Li) or alkylmagnesium halide (CH_3MgI) (Kim *et al*., 1993)
- oxidation of ethylpyridine using *tert*.-butylhydroperoxide and a chromium zinc hydrotalcite-like catalyst (Choudary *et al*., 1996)

2-Acetylpyridine is listed in the EPA's TSCA Inventory (STN International, 1996a). The EPA received no reports of 1993 annual production of Æ10,000 lbs. by U.S. manufacturers, according to Walker (1996). Nevertheless, 2-acetylpyridine 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 Reilly Industries, Inc.; 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. According to recent issues of chemical directories, 2-acetylpyridine is manufactured and/or distributed by Aldrich Flavors & Fragrances, Classic Flavors & Fragrances, Howard Hall International, Karl Industries, Inc., Penta Manufacturing Co., Pyrazine Specialties, Inc., Raschig Corp., Reilly Industries, Inc., SAF Bulk Chemicals, Schweizerhall, Inc. and Wall Chemical Corp. (Kuney, 1994; Hunter, 1995; Van, 1995).

Based on a survey conducted by the National Academy of Sciences (NAS), the Food and Drug Administration (FDA) estimated that Ç950 lbs. of 2-acetylpyridine was sold in the United States in 1987 for food flavoring use (Benz, 1996).

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1.9 x 10^{-2} ppm. It has been detected as a flavor or aroma constituent of various consumed food products; some sources include peppermint and spearmint oils, coriander oil, licorice extract, heated corn oil, roasted sesame seed oil, and beer and whiskey, in which pyridines are especially associated with off-flavor (STN International, 1996). 2-Acetylpyridine has been identified as a volatile Maillard reaction product thermally generated and released during corn flour extrusion cooking (Nair *et al*., 1994). Karahadian and Johnson (1993) compared the flavor characteristics of spray-dried masa flour, which requires extensive heat treatment during processing, and fresh-made masa dough; they reported concentration levels of 8 ppb of 2-acetylpyridine in dough from spray-dried masa flour and 2 ppb in tortillas made with fresh masa dough.

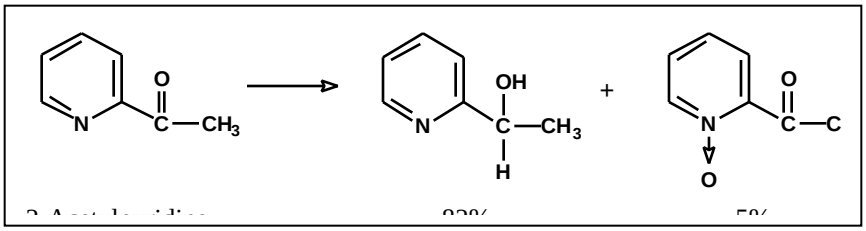
Environmental Occurrence: 2-Acetylpyridine has been identified in natural and processed food products. It has also been reported to occur as an environmental pollutant in wastewater and in urban air contaminated with tobacco smoke. Merli and coworkers (1981) reported 2-acetylpyridine to be present in the basic fraction of marijuana smoke condensate as well as in tobacco smoke. Rogge and coworkers (1994) have suggested its use as a marker molecule for the detection of air pollution by cigarette smoke.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace maximum allowable levels of 2-acetylpyridine. 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-Acetylpyridine is a "generally recognized as safe" (GRAS) substance approved by the FDA as a direct food additive (Posternak *et al*., 1975; FDA, 1996).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

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

Animal Data: No 2-year carcinogenicity studies of 2-acetylpyridine in animals were identified in the available literature. The following acute and subchronic toxicity



information was made available based on a search of the FDA's Priority-Based Assessment of Food Additives (PAFA) database (FDA, 1996):

- •lowest effect level (LEL) for all available rat and mouse studies: 330 mg/kg bw/day
- •highest no effect level (HNEL): 110 mg/kg bw/day
- •oral rat LD_{50}: 2,160 mg/kg bw
- •oral (gavage) rat subchronic (90 day) study: liver effects - necrosis; organ weight increase - spleen; proliferative effect - bile duct cellular hypertrophy

Short-Term Tests: Only one *in vitro* or *in vivo* study to assess genetic toxicity of 2-acetylpyridine was found in the literature. Zimmermann and coworkers (1986) reported this chemical to be one of a series of pyridine derivatives which was positive for induction of mitotic aneuploidy in *Saccharomyces cerevisiae*.

Metabolism: Takeshita and coworkers (1996) studied the biotransformation of 2-acetylpyridine in rat liver 9,000xg supernatant (S-9). They reported that during the metabolism of 2-acetylpyridine enantioselective reduction of the carbonyl group predominated over N-oxidation and did not involve cytochrome P-450. The metabolism of 2-acetylpyridine proceeded according to the following metabolic pathway with metabolite yields as shown.

Other Biological Effects: 2-Acetylpyridine exhibits very low teratogenicity when injected into chicken embryos. Caplan (1971) injected 2-acetylpyridine at doses up to 50 mg/egg on day 4.Up to 4 mg/egg did not cause recognizable teratogenic effects and levels of 12 mg or greater were fatal. A 8 or 10 mg/egg, a very low frequency of defects in the digits of the legs were found.

Landauer and Salam (1974) found that injection of 130 chicken embryos at 96 hours of incubation with 15 mg/egg 2-acetylpyridine produced among 107 survivors an incidence of 5.6% slight muscular hypoplasia. Following coadministration with 2.5 mg/egg ethionine, muscular hypoplasia was increased to 46.7% (24.4% slight, 22.2% marked or extreme), and beak deformities (short upper beak, 4.4%; short lower or parrot beak, 3.3%) and defective necks (3.3%) were observed among 90 survivors.

Administration of 2.5 mg/egg of ethionine alone produced muscular hypoplasia in 15.1% (14.2% slight; 0.9% marked or severe) and a lower incidence of short upper beak deformities (0.9% and a higher incidence of short lower or parrot beak deformities (5.7%). Landauer and Salam concluded that 2-acetylpyridine had very low teratogenicity but, in combination with ethionine, was highly synergistic for muscular hypoplasia.

Structure Activity Relationships: Six compounds structurally similar to 2-acetylpyridine were screened for relevant information associating these chemicals with a mutagenic or carcinogenic effect. A summary of information found in the available literature is presented in Table 1. No information was found on the carcinogenicity or mutagenicity of acetylpyrazine [22047-25-2] or methyl(2-pyridyl)carbinol [18728-61-5]. Mutagenicity data were available on four of the compounds, 3-acetylpyridine, 4-acetylpyridine, 2-acetylpyrrole, and acetophenone.

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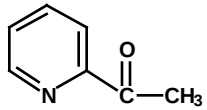
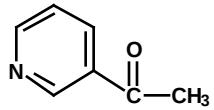
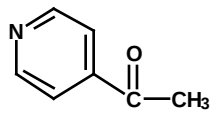
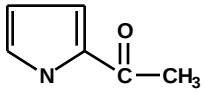
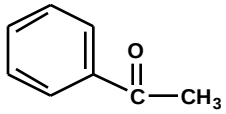
Table 1. Summary of Information on 2-Acetylpyridine and Related Compounds

Chemical Name	Carcinogenicity Data	Mutagenicity Data	Other
2-Acetylpyridine [1122-62-9] 	NDF	positive in *S. cerevisiae* for sex chromosome loss (Zimmermann *et al.*, 1986)	very low teratogenicity when injected into chicken embryos—a very low frequency of defects in the digits (Caplan, 1971); very low incidence of muscular hypoplasia but highly synergistic in combination with ethionine (Landauer & Salam, 1974)
3-Acetylpyridine [350-03-8] 	NDF	induced sister chromatid exchanges (SCEs) in Chinese hamster ovary cells (Oikawa *et al.*, 1980) positive in *S. cerevisiae* for sex chromosome loss and mitotic recombination (Zimmermann *et al.*, 1986) negative in *Escherichia coli* WP2 uvrA (Pai *et al.*, 1978) enhanced unscheduled DNA synthesis in human lymphocytes exposed to UV irradiation (Miwa *et al.*, 1981; Sims *et al.*, 1982)	low teratogenicity, as expressed by muscular hypoplasia, following single injection in chicken embryos; highly synergistic effect in combination with ethionine and suppressed in combination with nicotinamide (Caplan, 1971; Landauer & Salam, 1974)
4-Acetylpyridine [1122-54-9] 	NDF	negative in *Salmonella typhimurium* TA97, TA98, TA100, and TA1535 with and without metabolic activation (NTP, 1995; Zeiger *et al.*, 1992) positive in *S. cerevisiae* for gene conversion,	no teratogenicity in chicken embryos following single injection of doses up to 4 mg; 8 mg or higher was fatal (Caplan, 1971)

		mitotic recombination, sex chromosome loss, and nondisjunction (Zimmermann *et al.*, 1986; Whittaker *et al.*, 1989) positive in Chinese hamster ovary cells for induction of sister chromatid exchanges and chromosomal aberrations (Loveday *et al.*, 1990; NTP, 1995)	low teratogenicity, as expressed by beak deformities, following single injection in chicken embryos; highly synergistic effect in combination with ethionine for muscular hypoplasia (Landauer & Salam, 1974)

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

Chemical Name	Carcinogenicity Data	Mutagenicity Data	Other
2-Acetylpyrrole [1072-83-9] 	NDF	positive in *S. typhimurium* strain TA98 without metabolic activation; negative in TA100 with and without metabolic activation (Lee *et al.*, 1994; Wang *et al.*, 1994) extract of the reaction product with nitrite: positive in *S. typhimurium* strains TA97, TA98, TA100, TA102, and TA104 with and without metabolic activation (Yen & Lee, 1986)	
Acetophenone [98-86-2] 	no adverse effects in rats fed 10,000 ppm in the diet for 17 weeks (NLM, 1996)	negative in *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1535, TA1537, and TA2637 with and without metabolic activation (Florin *et al.*, 1980; Elliger *et al.*, 1984; Nohmi *et al.*, 1985; Fujita & Sasaki, 1987) negative in *Bacillus subtilis* rec assay (Oda *et al.*, 1978)	no change in the gestation period, size of litter, weight of the offspring, time for appearance of teeth or hair, opening of the eyes, or appearance of reflexes following dermal application to pregnant rats on days 10 through 15 of pregnancy (NLM, 1996)

		negative with nitrosation in SOS chromotest using *E. coli* strain PQ37 (Ohshima *et al.*, 1989) negative in an *E. coli* differential growth inhibition assay (Fluck *et al.*, 1976) positive for the induction of chromosomal aberrations in Chinese hamster lung cells with metabolic activation; negative without activation (Sofuni *et al.*, 1985)	

NDF = No data found

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