SUMMARY OF DATA FOR CHEMICAL SELECTION

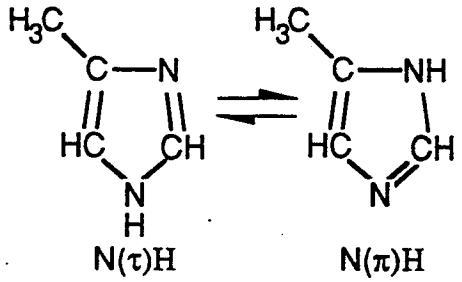
CHEMICAL IDENTIFICATION

CAS Registry Number: 822-36-6

Chem. Abstr. Name: 1H-Imidazole, 4-methyl (9 CI)

Synonyms and Trade Names: Imidazole, 4-methyl; 4(5)-methylglyoxaline; 4(or 5)-methylimidazole; 4(5)-methylimidazole; 4-methylimidazole; 5-methylimidazole; 4-MeI

Structure, Molecular Formula and Molecular Weight:



$C_4H_6N_2$ Mol. wt.: 82.11

Chemical and Physical Properties [From Heilbron (1988) unless otherwise specified]

Description:	Crystalline
Boiling Point:	263°C (The 1989-90 Chemalog)
Melting Point:	56°C (120-125°C @ 0.2 mm); 46-48°C (The 1989-90 Chemalog)
Solubility:	Soluble in water and alcohol
Stability:	Tautomer equilibrium constant, K_T= ≈1.3 (theoretical) (Worth, 1989) 1.5 in H_2O @ pH = 11.0
Density:	1.0416 g/cc (Weast, 1989)
Flash Point:	>112°C (235°F) (The 1989-90 Chemalog)

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Technical Products and Impurities: 2-Methylimidazole is available from four suppliers at 99% purity, with one supplier offering 98% purity. 4-Methylimidazole is typically available at 98% purity.

BASIS OF NOMINATION TO THE CSWG

2-Methylimidazole was among a broad selection of chemical substances brought to the Contract Support Planning Group (CSPG) in a class study of chemicals used in the electronics industry. In the preparation of a more detailed report of information on this compound, its positional isomer, 4-methylimidazole, came to attention as a toxicologically more active chemical and widely used, as well, particularly as a pharmaceutical intermediate. These two related compounds were considered to warrant nomination because of a lack of specific carcinogenicity test data in the literature combined with the potential for exposure by several possible routes.

SELECTION STATUS

ACTION BY CSWG: 12/14/90

Studies Requested: Carcinogenicity testing with high priority

Comments: In view of the widespread use and the potential for widespread exposure (in food products) to humans, 2-methylimidazole and 4-methylimidazole seem to be excellent candidates for nomination to the NTP. In addition, they have not been well tested. It was opined that from a structure-activity standpoint, one or the other of the compounds is likely to be carcinogenic.

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EXPOSURE INFORMATION

Commercial Availability:

Production and Producers: Several methods of preparation and numerous companies' patented syntheses were found in the literature for these compounds (STN on-line). A basic method for preparation of both compounds involves cyclocondensation of an aldehyde and ammonia with methylglyoxal. Variations include the use of ammonium carbonate or ammonium oxalate as the ammonia source (one author points out that the extremely hygroscopic nature of 4-methylimidazole dictates crystallization as the oxalate) and cyclocondensation of ammonia and formamide with hydroxyacetone. Other synthetic methods for one and/or the other of these two imidazoles include the following:

- 4-methylimidazole from propanol and formamide or by catalytic cyclization of bisformamidopropane;
- both by catalytic dehydrogenation of imidazoline derivatives;
- 4-methylimidazole by photolysis of alkenyltetrazole derived from alkenes by sequential epoxidation, ring opening and dehydration;
- 2-methylimidazole by platinum/alumina catalyzed cyclization of ethylenediamine with acetic acid (a recently published Russian method claiming to lower cost and simplify the purification process).

Companies which have patented one or more of the above synthetic methods in the last 10 years include BASF A.-G., Tasko Chemical Co., Ltd., Mitsui Toatsu Chemicals Ltd., Mitsui Petrochemicals Industry, Ltd.

No specific production data on these compounds was found in the literature [See Search Resource List]. Companies reported in published literature sources as domestic producers/suppliers of 2- or 4-methylimidazole are listed in Table 1.

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Table 1. Companies Reported to Produce/Supply 2-Methylimidazole or 4-Methylimidazole

Company	2 MeI	4 MeI
Aldrich Chemical Co.[a,b]	X	
Alfa Products/Morton Thiokol[a]	X	
American Tokyo Kasei, Inc.[a]	X	X
BASF Corp.[b]	X	X
Biddle Sawyer Corp.[b]	X	
C.I. Specialty Chemicals, Inc.[b]	X	
Chemical Dynamics Corp.[b]	X	X
Chemie Linz (USA)[b]	X	
Chem Service Inc.[a]	X	
Chugai International[b]		X
Coach Industries[b]		X
Davos Chemical Corp.[b,c]	X	
Eastman Kodak Co.[a]	X	
Fluka Chemical Corp.[a]	X	
Hexcel Corp.[c]		X
Janssen Chimica[a]	X	X
Jonas Chemical Corp.[b]		X
Maypro Industries, Inc.[b]	X	
Miki Sangyo (USA), Inc.[b]	X	
Pfaltz & Bauer, Inc.[a]	X	
Rhone-Poulenc[a]	X	
Riedel-de Haen[a]	X	
Sigma Chemical Co.[a]	X	X

[a] Fine Chemicals Database, DIAL File 360
[b] OPD Chemical Buyers Directory 1988
[c] Chemcyclopedia '89

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In addition to these reporting companies, several major chemical or pharmaceutical manufacturers are holders of patents which contain synthetic methods for the preparation of 2- or 4-methylimidazole. Among the patent holders are Air Products & Chemicals, Inc., BASF, A.-G.; Merck & Co., Inc.; and Toho Rayon Co., Ltd.

Drug companies active in drug design and research using these methylimidazoles, as evidenced by patent submissions, include: Shering Corp. (USA); Ciba-Geigy A.-G. (Germany); Mitsui Toatsu Chemicals, Inc. (Japan); Imperial Chemical Industries PLC (U.K.); Kuraray Co., Ltd (Japan); Janssen Pharmaceutica N.V. (Belgium); Bayer A.-G. (Germany); Dongting Pharmaceuticaol Factory (China).

Imported quantities reported in EPA's TSCA Plant and Production (TSCAPP) Database for 1977 are as follows:

2-Methylimidazole	
BASF Wyandotte Corp.	10,000 to 100,000 lbs
Ciba-Geigy Corp.	not reported
Dow Chemical Co.	not reported
Morton Chemical Co.	10,000 to 100,000 lbs
Okura & Co. (America), Inc.	1,000 to 10,000 lbd
Pennwalt Corp.	<1,000 lbs
Peter D. Olexy	<1,000 lbs
Rhone-Poulenc Inc.	10,000 to 100,000 lbs
Uniroyal Chemical Div.	<1,000 lbs

4-Methylimidazole	
BASF Wyandottte Cor.	<1,000 lbs

~~Use Pattern: Isomers, 2-methylimidazole and 4-methylimidazole, share a number of common uses, but each also has separate uses, more important for one than for the other. Principal~~

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Use Pattern: Isomers, 2-methylimidazole and 4-methylimidazole, share a number of common uses, but each also has separate uses, more important for one than for the other. Principal areas of use include:

- chemical intermediate/starting material or component in the manufacture of pharmaceuticals, photographic and photothermographic chemicals, dyes and pigments, and agricultural chemicals
- component of rubber compositions for property enhancement and heat stabilization.

Other areas of use or potential use include:

- component of resins and film used in dental filling and impression materials
- modifying agent/component of self-gelling liquid vehicle proposed for topical administration of medicaments, including fluoride to teeth
- corrosion inhibitors for protection of steel and non-ferrous alloys
- components of cleansing compositions such as oven cleaners and dry cleaning detergent

4-Methylimidazole is a major pharmaceutical intermediate; it is a starting material in the manufacture of cimetidine, a histamine antagonist widely used in ulcer therapy (Jacoby, 1980). According to Worth *et al.* (1989), cimetidine is one of two drugs accounting for the largest worldwide sales volumes (the other being ranitidine). Besides antiulceratives, 4-methylimidazole has been investigated for use as a starting material in the synthesis of cardiovascular stimulants, epoxy resin anticholesteremics, neurotransmitter antagonists, disinfectants/antiprotozoal antiseptic agents, and aromatase inhibitors investigated as possible antineoplastic agents. This compound is also used as a component of photographic color developing solutions, a component in imidazole-phenoxyalkanal oven cleaners, crosslinking agent for epoxy resin hardeners, chemical intermediate for production of fungicides, corrosion inhibitor for cooling water in heat exchange apparatus, component of absorbent to remove acid gases from hydrocarbon or synthesis gas, and starting material for inks and paper dyes.

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2-Methylimidazole, on the other hand, is used as a pharmaceutical intermediate but to a lesser extent than the 4(5)- substituted isomer. However, it is more widely used as a polymerization crosslinking accelerator and hardener for epoxy resin systems for semiconductor potting compounds and soldering masks. It is a component of numerous polymers including epoxy resin pastes, acrylic rubber - fluororubber laminates, films, adhesives, textile finishes and epoxy silane coatings. 2-Methylimidazole is also a photographic chemical component of both color and black and white film developing solutions and photothermographic color copying material as well as a starting material in the manufacture of thermal recording sheet for lithographic plate fabrication. It is used as a dyeing auxiliary for acrylic fibers and plastic foams.

Human Exposure: Based on data collected between 1972 and 1974, the National Occupational Hazard Survey (NOHS) reported that a total of 418 workers were potentially exposed to 2-methylimidazole. They represented 6 occupations at 676 facilities in 4 industries. The National Occupational Exposure Survey (NOES), 1983, reported that a total of 7,023 workers (including 3,073 women) in 22 occupations at 318 facilities in 11 industries were potentially exposed to 2-methylimidazole (RTECS on-line, 1990).

In addition to industrial exposures, humans may be exposed to low levels of either or both of these methylimidazoles in tobacco smoke (Sakuma *et al.*, 1984). Food consumption of some processed, treated or cooked foods may also be a source of low level human exposure to either one of these imidazoles which have been found to be undesirable toxic by-products formed in ammoniated molasses and caramel-colored syrups under certain conditions. 4-Methylimidazole, for example, has been reported to be one of several compounds resulting from the interaction of reducing sugars with ammonia. Nishie *et al.* (1970), concluded that 4-methylimidazole was the chief toxic factor leading to convulsant activity in cattle fed ammoniated molasses. Yoshikawa and Fujiwara (1981), used thin layer chromatography to determine levels of 4(5)-methylimidazole in food. Of the various

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kinds of foods in which they identified 4-methylimidazole, they found concentrations especially high in Worcestershire sauce, reporting an average recovery of 2.5 ppm for the 93 Worcestershire sauces analyzed.

Environmental Occurrence: Although not occurring normally in nature, 2-methylimidazole and 4-methylimidazole have been synthesized under plausible prebiotic conditions by Oro *et al.* (1984). These researchers have sought to show a link between these two imidazole derivatives and catalytic action involved in the synthesis of prebiological polymers. Both 2- and 4-methylimidazole have been identified as undesirable by-products in cigarette smoke and several products for food consumption including caramel coloring, soy sauce and wine. In addition, they have been identified as toxic by-products in ammoniated hay forage for livestock animals.

2- and 4-Methylimidazole have both been detected in mainstream (MS) and sidestream (SS) smoke from four types of cigarettes studied by Sakuma in 1984. Moree-Testa *et al.* (1984) identified 4(5)-methylimidazole as one of the two most abundant of 10 alkylated imidazoles in cigarette smoke. Ray *et al.* (1985), studied forage toxicity in livestock and identified both 2-methylimidazole and 4-methylimidazole as contributors of the methylimidazole content of ammoniated hay forage. Both were detected at concentrations ranging from 5 to 55 ppm.

Reports identifying methylimidazoles in caramel food color date back to the 1960s when 2-methylimidazole was found in industrial ammoniated caramel which was present in CocaCola and other products for human consumption. A joint committee of the UN's Food and Agriculture Organization recommended in 1971 that the daily intake of caramel should be restricted to no more than 100 mg/kg of body weight. An average adult would have to consume more than 2 liters of CocaCola a day to exceed this limit. A Danish law was

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enacted in August, 1976, restricting "the use of caramel coloring in food and beverages, citing a cancer risk".

Huang *et al.* (1983) found 4-methylimidazole at levels of ≈54 ppm in syrups produced by continuous process for making ammoniated catalyzed caramel colorant. Sweet potato starch was described as one starting material for industrial processing by ammonium to manufacture this caramel color food additive.

4-Methylimidazole has been identified as a hazardous reaction product in wine detectable to a threshold determination level of 0.5 ml caramel/liter wine and repeated alkalinization and extraction steps have been described for its removal (Huang 1981; Mattyasovszky and Jeszenszky, 1985). An analytical method for monitoring 4-methylimidazole content in soy sauce was described in a Chinese report (Huang, 1981).

2-Methylimidazole and 4-methylimidazole both formed in a model food system based on ammonium hydroxide, glycine and MSG as source materials and studied by Wong and Bernhard (1988). In a 1984 Japanese study of a cooked food model for the formation of cooked food flavor, 2-methylimidazole was identified as one of the heterocyclic compounds resulting from degradation of D-glucose through reaction with hydrogen sulfide, ammonia and the amino acids, cysteine and cysteamine (Sakaguchi, 1984).

Regulatory Status: No standards or guidelines have been set for occupational exposures or environmental levels of 2- or 4-methylimidazole.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiologic or case studies assessing human cancer risk in relation to 2- or 4-methylimidazole exposure were found in the published literature [See Search Resource List].

4-Methylimidazole is described as a toxic irritant by one manufacturer (The 1989-90 Chemalog).

No further information was found on the potential long term human effects or carcinogenic potential of either 2- or 4-methylimidazole in published literature sources [See Search Resource List].

Animal Data: No long term carcinogenicity studies were found in published literature sources for either of these imidazoles and there were no citations in PHS-149. 2-Methylimidazole and 4-methylimidazole have been associated with acute toxicity to foraging animals fed commercially ammoniated grasses or grains. Both 2- and 4-methylimidazole produced similar toxic neurologic effects in mice. They demonstrated convulsant activity; and 2-methylimidazole was less potent than 4-methylimidazole, which exhibited convulsant potency equivalent to about one quarter the potency of pentylenetetrazole, a known CNS stimulant. Other 4-methylimidazole-induced effects seen prior to convulsions included ≈50% reduction in spontaneous motor activity in treated mice and ≈1/3 reduction in heart rates of treated rabbits relative to controls with a 3-fold increase in respiration rate. Table 2 tabulates acute toxicity results for several animal species reported in this study (Nishie *et al.*, 1969).

In a study of "subacute toxicity" in the rat, Hidaka (1976), reported observing liver hypertrophy without disturbance of blood chemistries, after i.p. injection of an unspecified dose of 4-methylimidazole. In another study, Morgan and Edwards (1986), orally dosed

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female pregnant and postpartum cows and mice with 4-methylimidazole and found detectable levels of the chemical in the milk of lactating animals.

Table 2. Acute Toxicity Test Results for Lethality and Convulsant Effect

Compound	Species	Route	LD_{50},mg/kg	CD_{50},mg/kg
2 MeI	mouse	oral	1400	1300
2 MeI	mouse	i.p.	480	500
4 MeI	mouse	oral	370	360
4 MeI	mouse	i.p.	165	155
4 MeI	rabbit	i.p.	120	---
4 MeI	chicken	oral	590	---
4 MeI	chicken	i.p.	210	---

Both 2- and 4-methylimidazole acted synergistically when administered to 40 rats i.p. in combination with the antimigraine and prolactin inhibiting drug, lisuride. Both chemicals were administered at dosages too low to elicit the effects separately, but together they effected enhanced aggressive behavior in the animals (Ferrari *et al.*, 1987).

Neither 2-methylimidazole nor 4-methylimidazole is currently on test nor scheduled for testing in a standard carcinogenicity bioassay.

Short-Term Tests: No *in vitro* mutagenicity test results were found in the published literature for either 2- or 4-methylimidazole. Yamaguchi & Nakagawa (1983) studied the suppressing effects of some imidazoles, including 2-methylimidazole on the induced mutagenicities of several known mutagens (3-amino-1-methyl-5H-pyrido[2,3-b]indol, 2-acetylaminofluorene and benzo(a)pyrene which exert their mutagenic effect by metabolic activation. The test system was Ames *S. typhimurium* using strains TA98 and TA100. 2-

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Methylimidazole showed no significant reduction of His^+ revertant colonies, whereas 1-methylimidazole showed a marked suppressing effect. 4-Methylimidazole was not studied.

2-Methylimidazole was one of 114 compounds tested by Dierickx (1989) in an *in vitro* study to determine cytotoxicity as measured by cellular protein content in cultured Hep G2 cells. The PI_{50} for 2-methylimidazole was determined to be 18 mM (the concentration required to induce a 50% reduction in cell protein content). 2-Methylimidazole was two-and-one-half times more potent in exerting this cytotoxic effect than the parent compound imidazole, which had a PI_{50} of 45 mM.

DiMinno *et al.* (1982) studied several known inhibitors of thromboxane synthesis, including 4-methylimidazole, for effect on induction of platelet-fibrin clot retraction *in vitro*. Although 4-methylimidazole selectively inhibits the enzyme, thromboxane synthetase, it showed no inhibition of clot retraction.

Metabolism: Hidaka (1976), studied absorption, distribution, and excretion of 4-methylimidazole in the rat following i.p. administration of a single dose. Uptake at 5 min after injection was highest in the intestines followed by blood, liver, stomach, and kidney. Excretion mainly in the urine began ≈30 minutes after injection and reached approximately 90% after 4 to 8 hours.

Structure/Activity Relationships: Histamine and the amino acid histidine are 4(5)-substituted imidazoles related to 4-methylimidazole. Horton *et al.* (1983) found that 2-methylimidazole and 4-methylimidazole did not significantly affect human platelet aggregation *in vitro*, whereas imidazole and 1-methylimidazole showed inhibition of the rate of platelet aggregation. The authors concluded that the inhibitory effect attributed to some histamine H2 receptor antagonists containing the imidazole ring is not causally related to this common structural feature.

2-Methylimidazole and 4-methylimidazole were both studied for antioxidant activity in a 2,2'-azobis(2-amidinopropane dihydrochloride)(AAPH)-induced lipid oxidation system (Kohen *et al.*, 1988). 4-Methylimidazole showed 50% reduction in rate of phosphatidylcholine oxidation, and 2-methylimidazole showed 28% inhibition. In the same study, imidazole produced 39% inhibition, but 1-methylimidazole showed little antioxidant activity. The study was undertaken, according to the authors, to investigate the possible involvement of antioxidant activity in natural defense mechanism against active oxygen species.

In a study of *in vitro* antimicrobial activity of thirteen 2-alkylimidazole derivatives against 12 strains of gram positive or gram negative bacteria or yeasts, 1-dodecyl-2-methylimidazole and 2-undecylimidazole showed significant activity; and the authors concluded that especially 1-alkyl substitution but also 2-alkyl substitution on the imidazole ring influenced activity with a structure-activity based relationship. The introduction of a 3-alkyl substituent on the ring diminished activity, especially against yeasts (Shibata *et al.*, 1984).

According to Back and Tjia (1985), 4-methylimidazole inhibited tolbutanol hepatic metabolism *in vivo* in adult male Wistar rats, but 2-methylimidazole did not appear to inhibit the metabolism. They concluded that the inhibitory actions of substituted imidazoles *in vivo* were evidence for a structure-activity relationship.

Back *et al.* (1988), found that 4-methylimidazole acted as a non-competitive inhibitor of tolbutamide hydroxylase activity in human liver microsomes whereas 2-methylimidazole and 1-methylimidazole, also studied in the same test system, did not act as inhibitors. Such studies have pointed to the importance of the substituent position of the methyl group relative to biological activity of the compounds. Back and Tjia (1985) summarized the findings of other researchers and concluded that structure-activity studies have clearly shown that both cytochrome P-450 binding and inhibition are dependent on the presence of a sterically unhindered nitrogen atom at the 3-position of the imidazole ring and that inhibition

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results primarily from coordination of the non-bonded electrons at N-3 with the fifth or sixth ligand of the heme iron of cytochrome P-450.

Schuurman *et al.* (1988) found that 4-methylimidazole strongly stimulated the phosphorylation of rabbit kidney (Na^+ and K^+)-ATPase, while 2-methylimidazole did not. Grubmeyer *et al.* (1989) studied *S. typhimurium*-derived histidinal dehydrogenase (HDH) to elucidate the structure of the active site of the enzyme. High substrate specificity was investigated using histidinol analogues as competitive inhibitors and alternative substrates to map the functionally important binding interactions between substrate and enzyme. Imidazole and 4-methylimidazole were found to be competitive inhibitors of HDH vs. histidinol, but replacement by the 2-methyl analog resulted in a loss of binding strength.

No information was found in the published literature evaluating methyl-substituted imidazoles for carcinogenic potential relative to structure-activity. Based on the structure-activity studies cited above, it may be concluded that particularly the 4-methyl substituted imidazole has potential for long term adverse effects as a biologically active compound.

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SEARCH RESOURCE LIST

DIALOG	NLM	CIS	STN INTL
BIOSIS	EMICBACK	ENVIROFATE	BEILSTEIN
Enviroline (40)	RTECS	GENETOX	CA/CAOLD
Pollution Abstracts (41)	TOXLINE	SUSPECT	
World Textiles (67)	TOXLINE65	TSCAPP	
Sedbase (70)		TSCATS	
Embase (72,172,173)			
Int. Pharm. Abs. (74)			
Life Sciences Coll. (76)			
Chemical Exposure (138)			
Martindale Online (141)			
Medline (155)			
Cancerlit (159)			
NIOSH/OSHA (161)			
Chem Regs & Guidelines (174)			
Drug Info Full Text (229)			
De Haen Drug Data (267)			
Consumer Drug Info Full Text (271)			
Heilbron (303)			
Analytical Abstr. (305)			
Chem. Safety NewsBase (317)			
Chem. Bus. NewsBase (319)			
RTECS (336)			
Beilstein (390)			
PTS Newsletter (636)			
Federal Register (669)			

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