2-METHYLIMIDAZOLE

1. Exposure Data

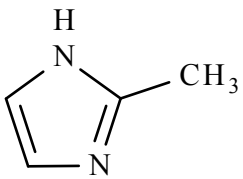
1.1 Chemical and physical data

From NTP (2004), GESTIS (2010) and HSDB (2010)

1.1.1 Nomenclature

Chem. Abstr. Services Reg. No.: 693-98-1
Chem. Abstr. Name: 2-Methylimidazole
Synonyms: 1*H*-Imidazole, 2-methyl-; imidazole, 2-methyl-; 2 methylglyoxaline
RTECS No.: N17175000
EINECS No.: 211-765-7

1.1.2 Structural and molecular formulae and relative molecular mass



$C_4H_6N_2$
Relative molecular mass: 82.11

1.1.3 Chemical and physical properties of the pure substance

Description: Colourless crystalline solid
Boiling-point: 267 °C
Melting-point: 142–145 °C.
Vapour pressure: 6.9×10^{-4} mm Hg at 25 °C (estimated)
Solubility: Soluble in water (8.09×10^4 mg/L at 25 °C, estimated); very soluble in ethanol
Flash-point: 155 °C
Autoignition: > 600 °C
Octanol/water partition coefficient: log K_{ow}, 0.24
pH value: 10.5–11.5 at 20 °C
Henry's law constant:
4.14×10^{-6} atm.m^3/mol at 25 °C

1.1.4 Technical products and impurities

No data were available to the Working Group.

1.1.5 Analysis

Ten alkylated imidazoles, including 2-methylimidazole, can be determined by high-performance liquid chromatography on LiChrosorb Si 60 after chemical derivatization with 4-chloro-7-nitro-benzo-2-oxa-1,3-diazole. This method is very selective because no sample clean-up procedure is necessary, and has been used to identify these chemical agents in cigarette smoke (Moree-Testa *et al.*, 1984).

1.2 Production and use

1.2.1 Production

A 1,2-dicarbonyl compound is condensed with an aldehyde and ammonia (R1 = H) in a molar ratio of 1:1:2, respectively (Radziszewski reaction). Replacement of a molar equivalent of ammonia with a primary amine (R1 = alkyl or aryl) leads to the corresponding 1-substituted imidazoles. The reaction is usually carried out in water or a water–alcohol mixture at 50–100 °C, and may involve such processes as distillation, extraction and crystallization. Distillation leads to imidazole with a purity > 99% (Ullmann's Encyclopedia of Industrial Chemistry, 2003, cited in HSDB, 2010).

In the United States of America, production volumes for 2-methylimidazole of < 500 000 pounds [226 800 kg] were reported in 2006 (HSDB, 2010).

1.2.2 Use

2-Methylimidazole is used as a raw material, a chemical intermediate, and as a component in the manufacture of pharmaceuticals, photographic and photothermographic chemicals, dyes and pigments, agricultural chemicals and rubber. It is also widely used as a polymerization cross-linking accelerator and a 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. It is also used as a dyeing auxiliary for acrylic fibres and plastic foams (NTP, 2004).

1.3 Occurrence

1.3.1 Natural occurrence

2-Methylimidazole is not known to occur as a natural product.

1.3.2 Occupational exposure

Workers may be potentially exposed to 2-methylimidazole by inhalation or dermal contact during its production and its use in the manufacture of pharmaceuticals, photographic and photothermographic chemicals, dyes, pigments, agricultural chemicals and rubber. It is also widely used in expoxy resin systems for semiconductor potting compounds (NTP, 2004). No recent information was found on the number of individuals occupationally exposed to 2-methylimidazole. The National Occupational Exposure Survey that was conducted from 1981 to 1983 estimated that 7023 workers were potentially exposed to 2-methylimidazole in the USA, including those employed in the following industries: chemicals and allied products, rubber and miscellaneous plastics products, primary and fabricated metals, machinery, electric and electronic equipment, transportation equipment, and instruments and related products (NIOSH, 1990).

1.3.3 Environmental occurrence

2-Methylimidazole may be released into the environment (e.g. ambient air, water and soil) via waste streams during its production and use.

HSDB (2010) reviewed information on and calculated parameters related to the environmental fate of 2-methylimidazole in ambient air, water and soil. 2-Methylimidazole is expected to exist only in the vapour phase and be degraded in the atmosphere by a reaction with photochemically produced hydroxyl radicals; its atmospheric half-life has been estimated to be

4.1 hours. It is not expected to undergo photolysis by sunlight.

2-Methylimidazole is not expected to adsorb to sediments and soils in the aquatic environment, but is expected to adsorb more strongly to soils that contain organic carbon and clay than to other types of soil in the terrestrial environment. In the soil, it is predicted to be highly mobile. Volatilization from water surfaces and moist soils is probable but not from dry soil surfaces. The half-lives for volatilization were 190 hours in a model river and 62 days in a model lake. Its potential bioconcentration in the aquatic environment is low, and its estimated bioconcentration factor in fish is 3.2 (reviewed by HSDB, 2010).

1.3.4 Occurrence in food

Exposure to 2-methylimidazole may occur through the consumption of foods contaminated as a result of the interaction of ammonia with reducing sugars. Forage, typically hay and straw, is sometimes treated with anhydrous ammonia (Waagepetersen & Vestergaard, 1977). Imidazoles and pyrazines appear to be the dominant groups of toxic by-products formed from the interaction of ammonia and reducing sugars. 2-Methylimidazole was identified in the plasma (0.005 µg/g) and milk (0.13 µg/g) of a sheep fed ammoniated forage (5.5 µg/g) (Sivertsen *et al.*, 1997), and in the ewe's lamb. It has also been found in the milk of cows fed ammoniated forage (Müller *et al.*, 1998).

2-Methylimidazole may also be formed during cooking when ammonium hydroxide, glycine and monosodium glutamine are present. In an experimental study that modelled cooking and the reaction of glucose, sodium, hydrogen and different nitrogen sources, large amounts (43.2% relative weight) of 2-methylimidazole were formed when glutamate was the nitrogen source (Wong & Bernhard, 1988).

1.3.5 Other occurrence

Exposure to 2-methylimidazole may occur from tobacco smoke. It was detected (concentration not reported) in sidestream and mainstream smoke (Moree-Testa *et al.*, 1984; Sakuma *et al.*, 1984).

1.4 Regulations and guidelines

No data were available to the Working Group.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Oral administration

See Table 3.1

3.1.1 Mouse

In a 2-year carcinogenicity study, groups of 60 male and 60 female B6C3F$_1$ mice were fed diets containing 0, 625, 1250 or 2500 ppm 2-methylimidazole (99.5% pure) for 105 weeks (equivalent to average daily doses of approximately 75, 150 or 315 and 80, 150 or 325 mg/kg body weight (bw) for males and females, respectively) (NTP, 2004; Chan *et al.*, 2008). Ten animals from each group were killed at 6 months for interim evaluation. The food consumption of exposed groups was generally similar to that of controls. 2-Methylimidazole caused increases in the incidence of thyroid follicular-cell adenoma, hepatocellular adenoma and hepatocellular carcinoma in male mice and of hepatocellular adenoma in female mice. The incidence of thyroid follicular-cell adenoma was significantly increased in male mice fed 2500 ppm. The incidence of hepatocellular

Table 3.1 Carcinogenicity studies of 2-methylimidazole administered in the diet to experimental animals

Species, strain (sex) Duration	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 105 wk	0, 625, 1 250 or 2 500 ppm 7 d/wk 60/group; 10 M and 10 F were necropsied at 6 mo for thyroid hormone analyses and histopathological evaluation.	Thyroid gland (follicular-cell adenoma): M[a]–0/50, 1/50, 0/50, 7/50 F–1/50, 0/50, 0/50, 1/50	$P = 0.006$ (high-dose M) $P < 0.001$ (trend M)	99.5% pure The mean body weights of 2 500-ppm males and females were 12% and 11% lower than those of the controls, respectively, at the end of the study.
		Liver (hepatocellular adenoma): M[b]–7/50, 14/50, 13/50, 18/50 F[c]–3/50, 4/49, 6/49, 10/50	$P = 0.005$ (high-dose M) $P = 0.006$ (trend M) $P = 0.037$ (high-dose F) $P = 0.015$ (trend F)	
		Liver (hepatocellular carcinoma): M[d]–4/50, 8/50, 14/50, 6/50	$P = 0.003$ (mid-dose M)	
		Liver (hepatocellular adenoma and carcinoma): M[e]–10/50, 22/50, 22/50, 22/50	$P = 0.09$ (low-dose M) $P = 0.002$ (mid-dose M) $P = 0.003$ (high-dose M) $P = 0.007$ (trend M)	
Rat, F344 (M, F) 106 wk	0, 300, 1 000 or 3 000 ppm (M) 0, 1 000, 2 500 or 5 000 ppm (F) 7 d/wk 60/group; 10 M and 10 F were necropsied at 6 mo for thyroid hormone analyses and histopathological evaluation.	**6 mo evaluation** Thyroid gland (follicular-cell adenoma): F–0/10, 0/10, 0/10, 2/10 (F)		99.5% pure Survival of 2 500-ppm females was significantly lower than that of the controls. The mean body weight of 2 500-ppm females was 12% lower than that of the controls at the end of the study; the mean body weights of 5 000-ppm females were significantly lower than those of the controls during most of the study. Serum concentrations of thyroid-stimulating hormone were increased at 6 mo in females. Dose-related increases in relative and absolute thyroid gland weights occurred at 6 mo in both sexes.
		2-yr evaluation Thyroid (follicular-cell adenoma): M–1/48, 0/46, 1/43, 3/50 F–0/49, 0/48, 0/42, 5/48	$P = 0.03$ (high-dose F) $P < 0.001$ (trend F)	

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 106 wk (contd.)		Thyroid (follicular-cell carcinoma): M–0/48, 2/46, 0/43, 2/50 F–1/49, 1/48, 1/42, 7/48	$P = 0.03$ (high-dose F) $P = 0.003$ (trend F)	
		Thyroid (follicular-cell adenoma and carcinoma): M[f]–1/48, 2/46, 1/43, 5/50 F[g]–1/49, 1/48, 1/42, 11/48	$P = 0.046$ (trend M) $P = 0.002$ (high-dose F) $P < 0.001$ (trend F)	
		Liver (hepatocellular adenoma): M–0/50, 1/50, 3/50, 1/50 F[h]–1/50, 0/49, 2/50, 4/50		
		Liver (hepatocellular carcinoma): M–0/50, 0/50, 1/50, 2/50		
		Liver (hepatocellular adenoma and carcinoma): M[i]–0/50, 1/50, 3/50, 3/50		

[a] Historical incidence (mean ± SD) for 2-yr feed studies in male mice: 3/309 (1.0 ± 1.0%), range 0–2%
[b] Historical incidence (mean ± SD) for 2-yr feed studies in male mice: 60/310 (19.0 ± 8.5%), range 10–30%
[c] Historical incidence (mean ± SD) for 2-yr feed studies in female mice: 29/309 (9.3 ± 2.4%), range 6–12%
[d] Historical incidence (mean ± SD) for 2-yr feed studies in male mice: 43/310 (13.7 ± 5.1%), range 8–20%
[e] Historical incidence (mean ± SD) for 2-yr feed studies in male mice: 95/310 (30.2 ± 10.4%), range 20–45%
[f] Historical incidence (mean ± SD) for 2-yr feed studies in male rats: 8/307 (2.6 ± 3.0%), range 0–8%
[g] Historical incidence (mean ± SD) for 2-yr feed studies in female rats: 3/309 (1.0 ± 1.1%), range 0–2%
[h] Historical incidence (mean ± SD) for 2-yr feed studies in female rats: 2/310 (0.6 ± 1.0%), range 0–2%
[i] Historical incidence (mean ± SD) for 2-yr feed studies in male rats:[d]7/310 (2.2 ± 2.0%), range 0–5%
d, day or days; F, female; M, male; mo, month or months; SD, standard deviation; wk, week or weeks; yr, year or years
From NTP (2004); Chan *et al.* (2008)

adenoma occurred with positive trends in male and female mice and was significantly increased in the 2500-ppm groups. The incidence of hepatocellular carcinoma was significantly increased in 1250-ppm males. The incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in all treated males, and that of hepatocellular adenoma in 2500-ppm males and females and hepatocellular carcinoma in 1250-ppm males exceeded the historical control ranges for feed studies.

[Tumours of the thyroid are rare spontaneous neoplasms in experimental animals.]

3.1.2 Rat

In a 2-year carcinogenicity study, groups of 60 male and 60 female F344/N rats were fed diets containing 0, 300, 1000 or 3000 ppm (males) and 0, 1000, 2500 or 5000 ppm (females) 2-methylimidazole (99.5% pure) for 106 weeks (equivalent to average daily doses of approximately 13, 40 or 130 and 50, 120 or 230 mg/kg bw for males and females, respectively) (NTP, 2004; Chan *et al.*, 2008). Ten animals from each group were killed at 6 months for interim evaluation. The food consumption of 3000-ppm males was lower than that of controls from week 4 through to week 28, and that of 5000-ppm females was lower throughout the study. 2-Methylimidazole caused increases in the incidence of thyroid follicular-cell adenoma and follicular-cell carcinoma in females and of thyroid follicular-cell adenoma or carcinoma (combined) in males. At the 6-month interim evaluation, thyroid follicular-cell adenomas occurred in two females exposed to 5000 ppm. At 2 years, increases with a positive trend were observed in the incidence of thyroid follicular-cell adenoma, follicular-cell carcinoma and follicular-cell adenoma or carcinoma (combined) in females, which were significant in the 5000-ppm group. The incidence of thyroid follicular-cell adenoma or carcinoma (combined) in males showed a positive trend and exceeded the historical control ranges. In exposed males and females, the incidence of some hepatocellular tumours (hepatocellular adenoma in females and hepatocellular adenoma or carcinoma combined in males) exceeded the respective historical control ranges and may have been related to exposure to 2-methylimidazole.

[Tumours of the thyroid are rare spontaneous neoplasms in experimental animals.]

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

(a) Absorption, distribution and excretion

Following intravenous administration of 3 µmol/kg bw [246.5 µg/kg bw] [^{14}C]2-methylimidazole to male Wistar rats, radioactivity associated with 2-methylimidazole and its metabolites was excreted in the urine. About 78% of the injected dose was excreted within 24 hours (Ohta *et al.*, 1998).

In male and female F344 rats, 2-methylimidazole was rapidly absorbed and widely distributed following either intravenous or oral administration by gavage (Johnson *et al.*, 2002). In male F344 rats, 90% of 2-methylimidazole was eliminated in the urine within 24 hours and about 4% in the faeces. The compound was not extensively metabolized and more than half of the dose was found in the urine as the parent compound. Tissue distribution was proportional to dose and independent of the route of administration (oral or intravenous) (Sanders *et al.*, 1998).

(b) Metabolism

Following intravenous administration, approximately 3% of a 3-µmol/kg bw dose was excreted by Wistar rats as the nucleophilic metabolite, 2-methylimidazolone. Pretreatment with the cytochrome P450 (CYP) inhibitors, SKF-252A or cimetidine, increased the amount of this urinary metabolite and the irreversible binding of 2-methylimidazole equivalents to the aortic connective tissue while both were decreased following pretreatment with triethylenetetramine dihydrochloride (TETA). TETA decreases the activity of copper-containing enzymes such as lysyl oxidase. This suggests that both CYP-dependent and -independent pathways are involved in the formation of this metabolite (Ohta *et al.*, 1998). A chemical model system for CYP has also been shown to oxidize 2-methylimidazole to 2-methylimidazolone efficiently (Miyachi & Nagatsu, 2002).

(c) Toxicokinetics

The toxicokinetics of 2-methylimidazole was characterized in male and female F344 rats (Johnson *et al.*, 2002) following intravenous (10 mg/kg bw) or oral administration by gavage (25, 50 or 100 mg/kg bw). The compound was rapidly absorbed and systemically distributed. Peak plasma concentrations were proportional to dose and were reached within 35–50 minutes While 2-methylmidazole was quickly eliminated, differences were noted between males and females. In males, clearance of all oral doses was similar to the rate observed following intravenous administration. In contrast, a decreased rate of clearance was observed in females at higher doses. Compared with the 25-mg/kg oral dose, clearance was 36 and 42% lower at 50 and 100 mg/kg, respectively. Nevertheless, the clearance value, although reduced in female rats at doses of 50 mg/kg or higher, was still greater than that obtained for intravenously or orally treated male rats. The data suggest that, at increased doses, renal clearance is saturated in female but not male rats.

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

The genetic effects of 2-methylimidazole have been reviewed (NTP, 2004).

(a) Mutations

2-Methylimidazole was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100 or TA1535 in the presence or absence of a metabolic activation system (detailed protocol presented by Zeiger *et al.*, 1988; NTP, 2004).

Yamaguchi & Nakagawa (1983) reported that 2-methylimidazole did not suppress the mutagenicity of 3-amino-1-methyl-5*H*-pyrido[2,3-*b*] indol, 2-acetylaminofluorene or benzo[*a*]pyrene in *S. typhimurium* strains TA98 and TA100. In contrast, imidazole and 1-methylimidazole decreased the mutagenicity of activation-dependent carcinogens such as benzo[*a*]pyrene and 2-acetylaminofluorene; the authors suggested that this was a consequence of the inhibition of metabolic activation of the procarcinogens.

(b) Chromosomal effects

The results of the induction of chromosomal damage by 2-methylimidazole *in vivo* were contradictory. When administered as three intraperitoneal injections at 24 hours intervals, 2-methylimidazole did not induce micronucleated polychromatic erythrocytes in the bone marrow of rats or mice 24 hours after the third injection (detailed protocol presented by Shelby *et al.*, 1993; NTP, 2004). However, after male and female mice were fed 2-methylimidazole in the diet for 14 weeks, a significant dose-related

increase in the frequency of micronucleated normochromatic erythrocytes and in the percentage of the micronucleated polychromatic erythrocytes was noted in the peripheral blood (detailed protocol presented by MacGregor *et al.*, 1990; NTP, 2004).

4.3 Mechanistic data

4.3.1 Effects on cell physiology

2-Methylimidazole induced thyroid lesions in rats and mice in both 15-day and 14-week feeding studies (NTP, 2004; Chan *et al.*, 2006). Both male and female F344 rats fed 3300 or 10 000 ppm for 15 days exhibited enlarged thyroid glands, hypertrophy of thyroid-stimulating hormone (TSH) cells and thyroid gland follicular-cell hyperplasia. After 14 weeks of exposure to doses greater than 2500 ppm, animals had significant decreases in triiodothyronine (T_3) and thyroxine (T_4) and an increase in TSH. Diffuse follicular hyperplasia was observed in males at 1250 ppm (80 mg/kg bw) and in females at 2500 ppm (160 mg/kg bw). Thyroid follicular adenoma was observed in two males in the 10 000-ppm (560 mg/kg bw) group. Testicular degeneration and a decreased spermatid count were also seen in this group. Females had increased length of the estrous cycle at 10 000 ppm (560 mg/kg bw). Minimal to mild anaemia was present in both sexes at the two highest exposure levels.

In male and female $B6C3F_1$ mice, 15 days of exposure to 2-methylimidiazole resulted in a dose-dependent increase in thyroid follicular-cell hypertrophy and haematopoietic cell proliferation in the spleen (Chan *et al.*, 2006). The incidence of thyroid, spleen and kidney lesions was dose-dependent in the 14-week study, and doses of 2500 ppm and higher induced thyroid gland follicular-cell hypertrophy in males and females. Haematopoietic cell proliferation in the spleen, anaemia and renal tubule pigmentation occurred in both males (1250 ppm and higher) and females (2500 ppm and higher).

The proposed mechanism for the hyperthyroid effects of 2-methylimidazole in rats appears to be indirect and results from effects of the compound on hepatic uridine diphosphate glucuronosyltransferase (UDPGT). 2-Methylimidazole induces a significant increase in UDPGT activity in the liver of rats. T_4 is glucuronidated in the liver and then excreted. Low levels of T_4 are consistent with the induction of UDPGT by 2-methylimidazole. Decreased T_4 results in increased TSH secretion that in turn causes thyroid follicular-cell hyperplasia, hypertrophy and ultimately tumours. In mice, the changes in circulating T_4 and TSH levels were less apparent, although hypertrophy was observed, which raises the possibility of another mechanism (Sanders *et al.*, 1998; NTP, 2004; Chan *et al.*, 2006).

4.3.2 Effects on cell function

Imidazole compounds can inhibit CYPs (Murray, 1987). Compared with imidazole, 2-methylimidazole was a less potent inhibitor of CYP2E1 (Hargreaves *et al.*, 1994).

After exposure of male and female rats to 2-methylimidazole in the diet, hepatic UDPGT activity was significantly increased for up to 6 months; relative liver weight was increased in treated males and females and total hepatic CYP level was generally decreased after 6 months (Chan *et al.*, 2008).

4.4 Mechanisms of carcinogenesis

In both F344/N rats and $B6C3F_1$ mice, 2-methylimidazole induced a dose-related increase in follicular-cell hyperplasia and hypertrophy in the thyroid. This effect was observed at the 6-month interim analysis, and was increased at the end of the 2-year carcinogenicity study. 2-Methylimidazole induced

thyroid follicular-cell adenoma or carcinoma (combined) and hepatocellular adenoma or carcinoma (combined) in male and female rats and mice (Chan *et al.*, 2008).

Hepatocellular neoplasms and thyroid follicular-cell neoplasms are often found in association in rodent carcinogenicity studies (Huff *et al.*, 1991; McConnell, 1992; Haseman & Lockhart, 1993). For chemicals that cause tumours in both the liver and thyroid, hepatic microsomal enzyme induction and thyroid hormone metabolism have been proposed as a possible mechanistic link that connects the pathogenesis of thyroid follicular tumours with that of hepatocellular neoplasms (McClain, 1989; McClain & Rice, 1999). 2-Methylimidazole induced increases in liver weights in mice and liver microsomal UDPGT activity in rats and mice. The increases, however, were not accompanied by changes in total hepatic CYPs in mice, and microsomal enzyme induction alone appeared to be insufficient to account for the thyroid and liver neoplasms in these studies (Chan *et al.*, 2008).

2-Methylimidazole in the diet induced micronucleated normochromatic erythrocytes in mice after 14 weeks of treatment, but not in the bone marrow of rats and mice after 3 days of treatment (NTP, 2004). A mutational mechanism may thus be involved in the carcinogenic effects of 2-methylimidazole observed in the liver and thyroid.

5. Summary of Data Reported

5.1 Exposure data

2-Methylimidazole is used as a raw material, chemical intermediate or component in the manufacture of pharmaceuticals, dyes, pigments and agricultural chemicals. Occupational exposure may occur by inhalation or dermal contact. In a model system, 2-methylimidazole was formed as a result of the interaction of ammonia with reducing sugars. It has been detected in ammoniated forage and ammoniated molasses used to feed animals, and in the milk from these animals. No data were available on the presence of 2-methylimidazole in commercial supplies of milk. 2-Methylimidazole has been detected in tobacco smoke.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

2-Methylimidazole was tested for carcinogenicity by administration in the diet to mice and rats. Oral administration of 2-methylimidazole caused an increased incidence of thyroid follicular-cell adenoma, hepatocellular adenoma and hepatocellular carcinoma in male mice, and of hepatocellular adenoma in female mice. It increased the incidence of thyroid follicular-cell adenoma and follicular-cell carcinoma in female rats, and of thyroid follicular-cell adenoma or carcinoma (combined) in male rats.

Tumours of the thyroid, which are consistently found in rats and mice, are rare spontaneous neoplasms in experimental animals.

5.4 Other relevant data

No data were available on the toxicokinetics of 2-methylimidazole in humans. After oral administration to rats, 2-methylimidazole was rapidly absorbed and widely distributed, and the parent compound and its metabolites were mainly excreted in urine. 2-Methylimidazole was not extensively metabolized in rats; 3% of the dose was excreted in the urine as 2-methylimidazolone. The formation of this metabolite involves both cytochrome P450-dependent and -independent pathways.

2-Methylimidazole was not mutagenic in bacteria, but induced micronuclei in polychromatic erythrocytes in mice after 14 weeks of administration in the diet, but not in rats or mice given three daily intraperitoneal injections. Thyroid lesions were induced by 2-methylimidazole in rats and mice in both 15-day and 14-week feeding studies. A possible indirect mechanism that causes these changes in the thyroid is the effect of 2-methylimidazole on hepatic uridine diphosphate glucuronosyltransferase.

There is weak evidence that enzyme induction is a mechanism by which thyroid and liver tumours develop in experimental animals. A genotoxic mechanism may also be involved in 2-methylimidazole-induced cancer in animals. The relevance of the tumour response in experimental animals to humans cannot be excluded.

6. Evaluation

6.1 Cancer in humans

No data were available to the Working Group.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-methylimidazole.

6.3 Overall evaluation

2-Methylimidazole is *possibly carcinogenic to humans (Group 2B).*

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