METHIMAZOLE

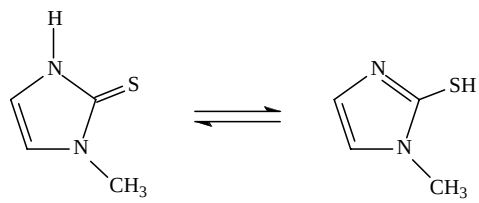
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 60-56-0
Deleted CAS Reg. Nos: 4708-61-6; 85916-84-3
Chem. Abstr. Name: 1,3-Dihydro-1-methyl-2*H*-imidazole-2-thione
IUPAC Systematic Names: 1-Methylimidazole-2-thiol; 1-methyl-4-imidazoline-2-thione
Synonyms: 2-Mercapto-1-methyl-1*H*-imidazole; 2-mercapto-1-methylimidazole; mercazolylum; 1-methyl-1,3-dihydroimidazole-2-thione; *N*-methylimidazolethiol; 1-methyl-2-imidazolethiol; 1-methyl-1*H*-imidazole-2-thiol; 1-methylimidazole-2(3*H*)-thione; 1-methyl-2-mercaptoimidazole; 1-methyl-2-mercapto-1*H*-imidazole; *N*-methyl-2-mercaptoimidazole; 1-methyl-2-thioimidazole; thiamazole

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_6N_2S$ Relative molecular mass: 114.17

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White to pale-buff, crystalline powder (Aboul-Enein & Al-Badr, 1979)
(*b*) *Boiling-point*: 280 °C (decomposes) (Lide & Milne, 1996)
(*c*) *Melting-point*: 146 °C (Lide & Milne, 1996)

(*d*) *Spectroscopy data*: Infrared [prism (20239, 57116), grating (18391, 57116)], ultraviolet (6780), nuclear magnetic resonance [proton (6068, 30101), C-13 (2452)] and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).

(*e*) *Solubility*: Very soluble in water (200 g/L); soluble in chloroform and ethanol; slightly soluble in benzene, diethyl ether and ligroin (Gennaro, 1995; Lide & Milne, 1996)

1.1.4 *Technical products and impurities*

Methimazole is available as 5- and 10-mg scored tablets (Gennaro, 1995).

Trade names for methimazole include Basolan, Danantizol, Favistan, Frentirox, Mercazole, Metazole, Metibasol, Metothyrine, Strumazol, Tapazole, Thacapzol, Thiamethazole, Thycapzol, Thyrozol and Tirodril (Budavari, 2000; Royal Pharmaceutical Society of Great Britain, 2000; Swiss Pharmaceutical Society, 2000).

1.1.5 *Analysis*

Several international pharmacopoeias specify infrared absorption spectrophotometry with comparison to standards and colorimetry as the methods for identifying methimazole; titration with sodium hydroxide is used to assay its purity and for its content in pharmaceutical preparations (The Society of Japanese Pharmacopoeia, 1996; AOAC International, 1998; US Pharmacopeial Convention, 1999).

Methods have been reported for the analysis of methimazole in biological fluids (blood, milk, serum, urine), tissues, incubation material and dried animal feed. The methods include capillary zone electrophoresis with ultraviolet detection, micellar electrokinetic chromatography, thin-layer chromatography, high-performance thin-layer chromatography, high-performance liquid chromatography (HPLC) with atmospheric pressure chemical ionization–mass spectrometry, reversed-phase HPLC with ultraviolet detection and gas chromatography with negative-ion chemical ionization–mass spectrometry (Moretti *et al*., 1986, 1988; Centrich Escarpenter & Rubio Hernández, 1990; Watson *et al*., 1991; De Brabander *et al*., 1992; Moretti *et al*., 1993; Batjoens *et al*., 1996; Blanchflower *et al*., 1997; Le Bizec *et al*., 1997; Buick *et al*., 1998; Vargas *et al*., 1998; Esteve-Romero *et al*., 1999).

1.2 Production

Methimazole can be prepared by reacting aminoacetaldehyde diethyl acetal with methyl isothiocyanate or by reacting thiocyanic acid with *N*-substituted amino acetals (Aboul-Enein & Al-Badr, 1979; Budavari, 2000).

Information available in 2000 indicated that methimazole was manufactured by three companies in China, two companies in Germany and one company each in Japan, Slovakia and Switzerland (CIS Information Services, 2000a).

Information available in 2000 indicated that methimazole was used in the formulation of pharmaceuticals by five companies in Taiwan, four companies in Germany, three companies in Turkey, two companies each in the Islamic Republic of Iran and Italy and one company each in Argentina, Austria, Belgium, Brazil, Canada, Denmark, Greece, Israel, Mexico, the Netherlands, Peru, the Philippines, Poland, Portugal, the Republic of Korea, Spain, Sweden, Thailand, the Ukraine, the USA and Venezuela (CIS Information Services, 2000b).

1.3 Use

Methimazole is used to control the symptoms of hyperthyroidism associated with Graves disease and to maintain patients in a euthyroid state for several years, until spontaneous remission occurs (American Hospital Formulary Service, 2000).

Methimazole is an anti-thyroid drug, developed in 1949, that is widely used in the treatment of hyperthyroidism. The usual starting dose is 10–30 mg/day, given orally as a single daily dose. Doses as high as 120 mg/day (20 mg every 4 h) may be used in severe thyrotoxicosis (‘thyroid storm’) (Cooper, 1998). Studies have shown better compliance with methimazole than with propylthiouracil (see monograph in this volume), most likely due to the single daily dose of the former (Nicholas *et al*., 1995). The long duration of action of methimazole makes multiple dosing unnecessary in the vast majority of patients (Roti *et al*., 1989). There are no intravenous preparations of methimazole, but it has been administered rectally to seriously ill patients who cannot take oral medications. The dose of methimazole is not different for infants, children or the elderly (Cooper, 1998), and it is considered unnecessary to alter the dose for patients with hepatic or renal disease (Cooper, 2000; see also section 4).

Carbimazole, the 3-carbethoxy derivative of methimazole, is converted to methimazole *in vivo*. It is also in widespread use as an anti-thyroid agent in Europe and Japan. In the USA, propylthiouracil is used as the primary therapy for hyperthyroidism in pregnancy, but methimazole or carbimazole is used as the first treatment in many parts of the world (Masiukiewicz & Burrow, 1999). The doses used are similar to those for non-pregnant women, with an effort to minimize them when possible to avoid fetal hypothyroidism. Methimazole is considered to be safe for use at low doses by lactating women (Azizi, 1996; Azizi *et al.*, 2000).

Anti-thyroid drugs, including methimazole, may be given for several weeks up to 1–2 years. After initiation of therapy, thyroid function improves slowly, returning to normal only by 6–12 weeks of treatment (Okamura *et al*., 1987). The time that it takes a patient to achieve a euthyroid state depends on a variety of clinical factors, including the severity of the hyperthyroidism at baseline, the size of the thyroid (correlated with intrathyroidal hormonal stores) and the dose of the anti-thyroid drug. Often, as thyroid

function improves, the dose of antithyroid drug can be reduced. For example, maintenance doses of methimazole of 2.5–5 mg/day may be adequate to control thyroid function for an extended period. Low doses of anti-thyroid drugs are most successfully used in areas of the world with marginal iodine sufficiency, as high intrathyroidal iodine concentrations would be expected to offset the effects of the drugs (Azizi, 1985).

Methimazole and carbimazole are also used to treat feline hyperthyroidism (Prince, 2000). Methimazole has been used illegally in cattle as a fattening agent (Martínez-Frías *et al.*, 1992).

Methimazole is also used in cyanide-free silver electroplating (Budavari, 2000).

1.4 Occurrence

1.4.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 2000) about 700 workers, including pharmacists, health aides and metal-plating machine operators, were potentially exposed to methimazole in the USA.

1.4.2 *Environmental occurrence*

No data were available to the Working Group.

1.5 Regulations and guidelines

Methimazole is listed in the pharmacopoeias of Italy, Japan, Poland, Taiwan and the USA (The Society of Japanese Pharmacopoeia, 1996; Wang *et al.*, 1998; US Pharmacopeial Convention, 1999; Royal Pharmaceutical Society of Great Britain, 2000) and is also registered for human use in the Netherlands, Portugal, Spain and Sweden (Instituto Nacional de Farmacia e do Medicamento, 2000; Medical Products Agency, 2000; Medicines Evaluation Board Agency, 2000; Spanish Medicines Agency, 2000).

2. Studies of Cancer in Humans

No information was available specifically on methimazole.

2.1 Cohort studies

Dobyns *et al.* (1974) followed up 34 684 patients treated in England and the USA for hyperthyroidism between 1946 and 1964, 1238 of whom had been treated for at least 1 year with unspecified anti-thyroid drugs. No malignant thyroid neoplasm was

found within 1 year of treatment. By 1968, more cases of thyroid neoplasm were found at follow-up among patients initially treated with anti-thyroid drugs (4 malignant tumours and 18 adenomas in 1238 patients) than among those initially treated with ^{131}I (19 malignant tumours and 41 adenomas in 21 714 patients) or (partial) thyroidectomy (4 malignant tumours and 14 adenomas in 11 732 patients). The authors suggested that more neoplasms were found in the drug-treated patients because subsequent thyroidectomy was more frequent in this group (30% of drug-treated patients, as compared with 0.5% of those initially treated with ^{131}I and 1.2% of those treated with primary thyroidectomy), which provided more opportunity for identification of neoplasms. [The Working Group noted that rates could not be calculated because person–years were not provided, and the ages of the groups were not given.]

Ron *et al*. (1998) updated the report of Dobyns *et al.* (1974) and followed-up 35 593 patients treated for hyperthyroidism between 1946 and 1964 in 25 clinics in the USA and one in the United Kingdom. By December 1990, about 19% had been lost to follow-up, and 50.5% of the study cohort had died. A total of 1374 patients (1094 women) had been treated with anti-thyroid drugs only, 10 439 (7999 women) with ^{131}I and drugs, 10 381 (8465 women) with thyroidectomy and drugs, 2661 (2235 women) with a combination of the three types of treatment and the remainder by other means. The drugs used during the study period were chiefly thiourea derivatives and iodine compounds. One year or more after the start of the study, the standardized mortality ratio (SMR) in comparison with the general population for the patients treated with anti-thyroid drugs only was 1.3 (95% confidence interval [CI], 1.1–1.6) for deaths from all cancers, which was chiefly due to significantly more deaths from oral cancer (4.2; 95% CI, 1.3–9.7; five cases) and brain tumours (3.7; 95% CI, 1.2–8.6; five cases). The excess risk for death from brain cancer persisted after exclusion of cases prevalent at the time of entry into the study. No deaths from thyroid carcinoma were recorded. The SMR for all cancers was approximately 1.0 in patients treated with ^{131}I or surgery (with or without anti-thyroid drugs), but the SMR for thyroid cancer was fourfold higher (3.9; 95% CI, 2.5–5.9; 24 cases observed) among patients who had been treated with ^{131}I with or without drugs. The authors noted that the group treated with drugs only was small; the type, quantity and dates of drug use were generally not available; and many patients had cancer before entry into the study, suggesting that some, but not all, of the excess could be attributed to the selection of patients with health problems for drug therapy. [The Working Group noted that the expected number of deaths from thyroid carcinomas was not reported, although it would almost certainly have been less than 1.0. Results were given for patients treated only with drugs but not for those given drugs with other treatment.]

2.2 Case–control studies

Ron *et al.* (1987) conducted a study of 159 cases of thyroid cancer and 285 population controls in Connecticut, USA, between 1978 and 1980. The use of anti-thyroid medications was not associated with an increased risk [relative risks not shown].

In a study carried out in northern Sweden between 1980 and 1989, 180 cases of thyroid cancer and 360 population controls were evaluated (Hallquist *et al*., 1994). Use of anti-thyroid drugs (two cases and two controls) was associated with a relative risk of 2.0 (95% CI, 0.2–21).

3. Studies of Cancer in Experimental Animals

Studies on the carcinogenicity of anti-thyroid chemicals, including methimazole, in experimental animals have been reviewed (Paynter *et al*., 1988).

3.1 Oral administration

Mouse: Groups of 78 male and 104 female C3H mice, 2 months of age, received methimazole (pharmaceutical grade) in their drinking-water at a starting dose of 35 mg/L, increased gradually over 26 months to 500 mg/L, when the study was terminated. The control groups comprised 57 male and 81 female untreated mice. No statistically significant increase in the incidence of tumours was seen at any site. An increased incidence of hyperplasia of thyroid gland epithelium in treated mice was described, but the actual incidences were not provided (Jemec, 1970).

Groups of 40 male and 35 female C3H/FIB mice, 2 months of age, received methimazole [purity not specified] at a dose of 250 mg/L of demineralized water in conjunction with a low-iodine pelleted diet (iodine content, 90 μg/kg) for up to 22 months. [The Working Group noted that this concentration of iodine in the diet was 10–30 times lower than that in standard diets used in carcinogenicity studies.] The concentration of methimazole was increased to 500 mg/L when the mice were 4 months old. Groups of 50 male and 50 female mice fed the low-iodine diet served as untreated controls. In addition, groups of 80 male and 108 female mice received methimazole in the drinking-water in conjunction with a high-iodine diet (iodine content, 9–10 mg/kg), the starting dose being 35 mg/L of water, increased gradually over 26 months to 500 mg/L. [The Working Group noted that this concentration of iodine in the diet was 3–10 times that in standard diets used in carcinogenicity studies.] Groups of 236 male and 239 female mice fed the high-iodine diet served as untreated controls. A statistically significant increase ($p < 0.01$) in the incidence of thyroid follicular-cell adenomas was reported over four periods of observation in the methimazole-treated mice on a low-iodine diet, the incidence being 7/75, including 3/75 in which pulmonary metastases were found. In contrast, the incidences of

adenomas in untreated controls on a low-iodine diet or a high-iodine diet and in the methimazole-treated group on a high-iodine diet were 1/150, 0/249 and 0/118, respectively (Jemec, 1977).

Rat: Groups of 25 male and 25 female rats (obtained from Harlan Industries, Cumberland, IN, USA), weighing 86–136 g [age not specified] were given diets containing methimazole (stated as pure) at concentrations of 5, 30 or 180 mg/kg of diet (equivalent to 0.25, 2.5 or 9.0 mg/kg bw per day) for 2 years. The control groups, consisting of 50 males and 50 females, received the diet without methimazole. Survival was poor in the group at the highest dose, the mortality rate being 50% in the first year (compared with < 10% in the other groups), and only 6% were still alive at 2 years, compared with 16–20% in the other groups. The incidence of thyroid follicular-cell tumours was increased at the two higher doses, the incidences for follicular adenoma in males and females combined being 1/55 (2%), 1/8 (13%), 31/55 (56%) and 17/32 (53%) at 0, 5, 30 and 180 mg/kg of diet, respectively [statistical significance not stated], the denominators representing the number of rats surviving when the first tumour was detected in each group. A treatment-related increase in the incidence of follicular adenocarcinoma was found in survivors, the incidences for males and females combined being 1/17 (6%), 5/42 (12%) and 5/24 (21%) at 0, 30 and 180 mg/kg of diet, respectively. The incidence of thyroid follicular hyperplasia was increased in both males and females receiving methimazole at 30 and 180 mg/kg of diet (Owen *et al*., 1973). [The Working Group noted the inconsistency in the sizes of the groups with thyroid tumours, particularly those with adenomas at 30 mg/kg of diet.]

3.2 Administration with known carcinogens

Rat: In medium-term initiation–promotion bioassays, groups of 20 male Wistar rats were given *N*-nitrosoethyl-*N*-hydroxyethylamine as an initiating agent and either trisodium nitrilotriacetate, hydroquinone or potassium dibasic phosphate as the promoting agents, and the effects of methimazole on renal tumour induction were tested. Rats initiated with the nitrosamine underwent nephrectomy of the left kidney and were fed the renal tumour promoters, either alone or in combination with methimazole, in the diet for 20 weeks at concentrations of 1% for trisodium nitrilotriacetate, 2% for hydroquinone, 10% for potassium dibasic phosphate and 300 mg/kg of diet for methimazole. Although methimazole reduced the incidences of renal tubule hyperplasia in each group, it had no effect on the incidence of renal tumours (Konishi *et al*., 1995).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Jansson *et al*. (1985) studied the pharmacokinetics of methimazole in healthy, thyrotoxic and hypothyroid persons before and after therapeutic doses for the treatment of euthyroidism. The initial distribution half-time of methimazole was reported to be 0.10–0.23 h, with an elimination half-time of 4.9–5.7 h after intravenous administration. Almost complete oral absorption was observed, with an absolute bioavailability of 93% in fasting persons. There were only minor interindividual variations in the pharmacokinetics, with the exception of one hypothyroid patient who showed a rapid elimination half-time in both the hypothyroid and euthyroid states (2.6 and 2.4 h, respectively). Hengstmann and Hohn (1985) reported elimination half-times of 2–3 h in euthyroid subjects and ~6 h in hyperthyroid patients. The elimination rate was lower in the hyperthyroid patients than in euthyroid subjects and was not restored when normal thyroid function was achieved. Although renal insufficiency had no effect, patients with hepatic failure had a prolonged elimination half-time of methimazole, the prolongation being proportional to the degree of impairment (Jansson *et al*., 1985). In hyperthyroid patients receiving carbimazole (1-methyl-2-thio-3-carbethoxyimidazole; see section 1) who then underwent thyroidectomy, the intrathyroidal concentration of methimazole was 518 ng/g of thyroid tissue 3–6 h after administration (Jansson *et al*., 1983).

The concentrations of methimazole were measured in blood and milk from five lactating women after oral administration of 40 mg of carbimazole, which is rapidly and completely transformed to methimazole. After 1 h, the mean concentrations of methimazole had reached 253 μg/L in serum and 182 μg/L in milk. Methimazole was not bound to protein in the serum, and its concentration in serum was comparable to that in milk. The total amount of methimazole excreted in milk over 8 h was 34 μg (range, 29–47 μg) or about 0.14% of the dose administered (Johansen *et al*., 1982).

In isolated, perfused, term human placentae, methimazole at doses of 1.5 and 15 μg/mL in either a protein-free perfusate (low dose only) or a perfusate containing 40 g/L bovine albumin readily crossed the placenta and reached equilibrium within 2 h. The transfer of methimazole was similar to that of propylthiouracil (see monograph in this volume; Mortimer *et al*., 1997).

4.1.2 *Experimental systems*

In studies in which radiolabelled methimazole was administered to Sprague-Dawley rats intravenously, intraperitoneally or orally (the drug was reported to be

completely absorbed after oral administration), about 5% was found to be bound to plasma proteins, and it seemed to be ubiquitously distributed to all tissues studied, although Pittman *et al*. (1971) reported that the thyroid and adrenal glands had the highest organ:plasma ratios. Approximately 10% of the administered radiolabel appeared in the bile, whereas 77–95% was excreted into the urine, with negligible amounts in the faeces, suggesting enterohepatic circulation. The half-time of urinary excretion of radiolabel was 5–7 h, regardless of the route of administration. Of the total radiolabel excreted in the urine, 14–21% was associated with unchanged drug. The major urinary and biliary metabolite was methimazole glucuronide (36–48%), and three other unidentified metabolites were found in the bile (Sitar & Thornhill, 1973; Skellern *et al*., 1973; Skellern & Steer, 1981).

Lee and Neal (1978) demonstrated that incubation *in vitro* of methimazole with rat hepatic microsomes led to the formation of 3-methyl-2-thiohydantoin and *N*-methylimidazole. They also showed that radiolabelled methimazole bound to microsomal macromolecules and that this binding was stimulated by NADPH. The cytochrome P450 and flavin-containing monooxygenase systems of rat hepatic microsomes have been implicated in these reactions (see section 4.2.2).

4.1.3 *Comparison of animals and humans*

In humans and rodents, methimazole is readily absorbed and rapidly excreted with a half-time of 5 h. In rats, glucuronidation is the main metabolic pathway; less is known about the metabolism of methimazole in humans.

4.2 Toxic effects

4.2.1 *Humans*

(*a*) *Effects on thyroid function at therapeutic doses*

Methimazole is commonly used to treat hyperthyroidism. It inhibits intrathyroidal synthesis of thyroid hormones by interfering with thyroid peroxidase-mediated iodine utilization. As a result, the concentrations of thyroxine (T4) and triiodothyronine (T3) in serum are decreased (Cooper, 2000). In some studies, hyperthyroid patients became hypothyroid if the dose of methimazole was not monitored carefully. In one study, 100% of patients became hypothyroid within 12 weeks while taking 40 mg/day (Kallner *et al*., 1996).

(*b*) *Other studies in humans*

Most of the toxic effects of methimazole are considered to be allergenic, including fever, skin rashes and arthralgia. Agranulocytosis is the most significant major side-effect, occurring in 4 of 13 patients investigated in one study. Cholestatic jaundice is a rare severe side-effect (Vitug & Goldman, 1985). The side-effects of methimazole

appear to be dose-related (Cooper, 1999). In a study of the toxic effects of methimazole in hyperthyroid patients receiving high daily doses of 40–120 mg, the major effects were agranulocytosis, granulocytopenia and abnormal liver function in 3% of patients, whereas 13% showed minor effects such as arthralgia, skin rash and gastric intolerance (Romaldini *et al.*, 1991). Other reports also indicate that rashes and agranulocytosis are the major side-effects (Wiberg & Nuttall, 1972; Van der Klauw *et al.*, 1999). At high doses (up to 120 mg/day), the incidence (32%) and severity of side-effects were increased (Wiberg & Nuttall, 1972; Meyer-Gessner *et al.*, 1994).

Methimazole therapy induced changes in plasma lipid peroxidation and the antioxidant system in hyperthyroid and euthyroid patients. Lipid peroxide plasma concentrations were decreased while ascorbic acid and vitamin E levels were significantly increased in euthyroid patients in comparison with hyperthyroid patients. Plasma glutathione peroxidase activity was increased and glutathione transferase activity was significantly decreased after euthyroidism was sustained with methimazole therapy (Ademoglu *et al.*, 1998).

Thyroglobulin mRNA levels and accumulation of thyroglobulin in the culture medium were enhanced by addition of methimazole to the Fischer rat thyroid cell line 5. The effect on *Tg* gene expression was independent of thyroid-stimulating hormone (TSH) or insulin concentrations, and methimazole did not alter TSH-induced cAMP production. Both iodide and cycloheximide (a protein synthesis inhibitor) inhibited the stimulatory effects of methimazole on protein synthesis (Leer *et al.*, 1991).

4.2.2 *Experimental systems*

Male marmosets (*Callithrix jacchus*) were given methimazole at an oral dose of 10 or 30 mg/kg bw per day for 4 weeks. Marked hypertropy of follicular epithelial cells was observed, with a significant decrease in the plasma T4 concentration. Hypertrophied epithelial cells were filled with dilated rough endoplasmic reticulum and reabsorbed intracellular colloid, with vacuoles that were positive to anti-T4 immunostaining (Kurata *et al.*, 2000).

Hood *et al.* (1999) examined the effect in rats of various concentrations of methimazole in the diet. The concentrations of total and free T4 were reduced by more than 95% after 21 days of treatment with increasing dietary concentrations of 30, 100, 300 and 1000 ppm (mg/kg), and those of total and free T3 were reduced by 60%. Feeding rats with diets containing 30 ppm (mg/kg) methimazole for 21 days resulted in a 5.6-fold increase in TSH, a 14-fold increase in thyroid follicular-cell proliferation and a twofold increase in thyroid weight. The increases in thyroid weight and follicular-cell proliferation were significantly correlated with the increase in TSH.

Administration of methimazole at a concentration of 0.05% in the drinking-water for 32 days to male Sprague-Dawley rats decreased the serum concentrations of T3 (by 80%) and T4 (by 90%) and also decreased the rate of body-weight gain, colonic temperature, systolic blood pressure and heart rate when compared with vehicle-treated rats

(Bhargava *et al*., 1988). Methimazole given in combination with DL-buthionine sulfoximine, an inhibitor of glutathione synthesis, caused centrilobular necrosis of hepatocytes and increased hepatic serum alanine aminotransferase activity in male ICR mice. Methimazole given to mice with normal levels of glutathione produced only a marginal increase in serum alanine aminotransferase activity and was not hepatoxic. Pretreatment with hepatic cytochrome P450 monooxygenase inhibitors prevented or at least greatly reduced the hepatotoxicity of methimazole in combination with DL-buthionine sulfoximine. Competitive substrates for flavin-containing monooxygenases also eliminated the hepatotoxicity of the two compounds in combination, indicating that methimazole is metabolized to an active hepatotoxicant by both cytochrome P450 monooxygenases and flavin-containing monooxygenases, and that inadequate rates of detoxication of the resulting metabolite(s) are responsible for the hepatotoxicity in glutathione-depleted mice (Mizutani *et al*., 1999).

Methimazole was toxic to the olfactory system in Long-Evans rats given a single intraperitoneal dose of ≥ 25 mg/kg bw or an oral dose of ≥ 50 mg/kg bw. A 300-mg/kg bw intraperitoneal dose resulted in almost complete destruction of the olfactory epithelium (Genter *et al.*, 1995). Bergman and Brittebo (1999) reported that [^{3}H]methimazole given to NMRI mice by intravenous injection showed selective covalent binding to Bowman glands in the olfactory mucosa, bronchial epithelium in the lungs and centrilobular parts of the liver. Extensive lesions of the olfactory mucosa were observed after two consecutive intraperitoneal doses of methimazole, but these were efficiently repaired within 3 months. Pretreatment with T4 did not protect against toxicity, but pretreatment with metyrapone (a cytochrome P450 inhibitor) completely prevented methimazole-induced toxicity and covalent binding in the olfactory mucosa and bulb.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

Pregnancy outcomes after use of methimazole during gestation have been reviewed. No differences in the rates of malformations were seen in the infants of hyperthyroid mothers who had and had not taken methimazole; however, 17 cases of aplasia cutis congenita were found in the offspring of women who had used methimazole. The authors estimated an expected incidence of 9.4 cases on the basis of the overall incidence of hyperthyroidism during pregnancy, the prevalence of methimazole use by hyperthyroid patients and the background incidence of the effect. They also reported that no signs of intellectual impairment were found in four studies involving 101 children whose mothers had undergone thioamide therapy (Mandel *et al*., 1994). Other cases of aplasia cutis have been reported in infants whose mothers were treated with methimazole during pregnancy (Sargent *et al*., 1994; Vogt *et al*., 1995). Martínez-Frías *et al*. (1992) suggested that an increase in the incidence of aplasia cutis noted

between 1980 and 1990 in the Spanish Collaborative Study of Congenital Malformations might have been due to illicit use of methimazole in animal feed, although no actual exposure was confirmed in this report. In contrast, no significant increase in the overall incidence of congenital malformations was noted in 36 women on methimazole therapy, and, in particular, no scalp defects were observed in the exposed infants (Wing *et al*., 1994). Similarly, a review of nearly 50 000 pregnancies in the Netherlands found no association between exposure to methimazole and defects of the skin or scalp (Van Dijke *et al*., 1987). An association between use of methimazole and choanal and oesophageal atresia has also been reported (summarized by Clementi *et al*., 1999).

Thyroid status at delivery was evaluated in the infants of 43 women who had been treated with methimazole for Graves disease for at least 4 weeks during pregnancy and compared with that of the infants of 32 women with no history of thyroid problems. The doses ranged from 2.5 to 20 mg/day. No difference was found in the mean concentration of free T4 or TSH in the cord blood of infants in the two groups. A similar lack of effect was seen in 34 women treated with propylthiouracil (see monograph in this volume; Momotani *et al*., 1997).

4.3.2 *Experimental systems*

Postnatal neurological development was evaluated in the offspring of groups of eight Sprague-Dawley rats given drinking-water containing methimazole at a concentration of 0 or 0.1 g/L from day 17 of gestation to postnatal day 10. The growth of offspring was reduced relative to that of controls after postnatal day 2, and they showed significant delays in acquisition of the surface-righting response (at 14 days *vs* 7 days in controls), auditory startle reflex (at 18 *vs* 12 days) and eye opening (at 17 *vs* 15 days). They also showed a significant reduction in locomotor activity in a 10-min open-field test at 21 days (Comer & Norton, 1982). In a study of the same design, 6-week-old, 4-month-old and 6-month-old rat offspring showed a pattern of relative decreases in locomotor activity in a residential maze, the result of a lack of habituation and a lack of a diurnal motor pattern. The treated offspring also had an asymmetric walking gait and alterations in exploratory patterns in a radial-arm maze. The two sexes were affected equally in all measures (Comer & Norton, 1985).

In groups of three Wistar rats given drinking-water containing methimazole at a concentration of 0 or 0.025% from day 8 of gestation, the total serum T3 and T4 concentrations were significantly reduced on day 18 of gestation, but fetal body weights were not affected nor were there any changes in the histological appearance of the testes. Treatment of offspring with 0 or 0.05% methimazole in the drinking-water from birth onwards significantly reduced the total serum concentrations of T3 and T4 at 21 and 50 days of age and reduced both body-weight gain and testis weight. [These rats were not old enough for the enlarged testes and enhanced sperm production observed in rats similarly treated with propylthiouracil (see monograph in this volume) to be seen]. Serum follicular-stimulating hormone and luteinizing

hormone concentrations were reduced at 35 and 50 days of age. The hypothyroid rats showed delayed maturation of the testes, as seen by a decrease in the diameter of the seminiferous tubules and a reduction in the number of germ cells per cross-section. Sertoli cells also showed retarded development. With the exception of the reduction in total T4 concentration, the effects were reversible by concomitant administration of L-T3 (100 μg/kg bw every other day) (Francavilla *et al*., 1991).

The teratogenic potential of methimazole was compared with that of ethylenethiourea (see monograph in this volume) in rat embryo cultures. Exposure of 9.5-day-old Wistar rat embryos to methimazole at a concentration of 100 μmol/L for 48 h did not affect the morphology of the embryos, but at 500 μmol/L the mean apparent embryonic age and somite number were statistically significantly lower than those of controls. At higher concentrations (1, 2 and 5 mmol/L), the yolk-sac diameter and crown–rump length were also lower ($p < 0.05$) than those of controls. While some similarities in embryonic responses were noted, the failure of closure of the cranial region in many embryos exposed to methimazole was not seen in embryos exposed to ethylenethiourea, and other effects seen in ethylenethiourea-exposed embryos were not seen in those exposed to methimazole (Stanisstreet *et al*., 1990).

The effect of methimazole-induced hypothyroidism during the neonatal period on testicular development was studied in Sprague-Dawley rats. Dams were given 0 or 0.025% methimazole in the drinking-water for 25 days from the day of parturition. Only male offspring were maintained in the litters [number of litters per group not specified]. Serum thyroid hormone concentrations were depressed at 25 days of age, but were normal by day 45. Body-weight gain was reduced early in life and remained 11% lower than that of controls at 90 days of age. At 90 days of age, the testis weights were increased by 18%, and daily sperm production was slightly increased. The effects were largely equivalent to those obtained after exposure to 0.004% propylthiouracil during the same neonatal period (Cooke *et al*., 1993).

Postnatal development of Swiss Webster mice was examined after administration of 0 (10 dams) or 0.1 g/L (12 dams) methimazole in the drinking-water from day 16 of gestation through day 10 of lactation. There was no effect on litter size at birth. Body weights were reduced through young adulthood, after which the effect was no longer significant. Developmental milestones (incisor eruption, eye opening, vaginal opening, testis descent) were unaffected. Surface–righting time (tested on days 7–11), negative geotaxis (tested on days 6, 8 and 10) and swimming ontogeny (tested on days 4–20) were affected by exposure. There were no effects on rotarod performance on day 52 or on brain weights on day 120 (Rice *et al*., 1987).

Neurological effects were studied in Fischer 344 rats exposed to methimazole in the drinking-water from gestational day 17 through lactational day 10 at a dose of 0, 0.01, 0.03 or 0.1 g/L, with approximately 12 litters per group. A number of indicators of neurological maturation, behaviour, thermoregulation, neurophysiology and morphology were measured at various ages. Pup weight (day 4), age at incisor eruption, thyroid histopathology (day 11), flash-evoked potential (day 14) and somatosensory-

evoked potentials in the 60–120-Hz range (day 90) were significantly altered at all doses. Thermoregulation (day 12) was reduced and kidney weights increased (day 11) at concentrations ≥ 0.03 g/L. Body weight (day 12) and auditory brainstem responses (day 90) were affected at the highest concentration. Body weights on day 14 were normal in all treated groups (Albee *et al*., 1989).

4.4 Effects on enzyme induction or inhibition and gene expression

No data were available to the Working Group.

4.5 Genetic and related effects

4.5.1 *Humans*

No data were available to the Working Group.

4.5.2 *Experimental systems* (see Table 1 for references)

Methimazole did not induce forward mutation in a fluctuation test with *Klebsiella pneumoniae*.

Methimazole induced chromosomal aberrations in a cell line derived from mouse mammary carcinoma and inhibited cell-to-cell communication in a primary culture of rat thyrocytes. Incubation of methimazole-treated thyrocytes from Sprague-Dawley rats with TSH did not affect the inhibitory effects of methimazole on gap-junctional intercellular communication.

No chromosomal aberrations were induced in bone-marrow cells, spermatogonia or primary spermatocytes of mice treated subcutaneously with methimazole for up to 5 days. The bone-marrow cells from these mice did not contain micronuclei. The frequency of sister chromatid exchange was increased in T lymphocytes of mice given 0.1% methimazole in the drinking-water for 2–6 weeks.

Subcutaneous injection of methimazole did not induce dominant lethal mutations in male mice.

4.6 Mechanistic considerations

Methimazole belongs to a class of drugs used in the treatment of hyperthyroidism, which act by interfering with the functioning of thyroid peroxidase. The mode of action in experimental animals is inhibition of thyroid peroxidase, which decreases thyroid hormone production and increases cell proliferation by increasing the secretion of TSH. This is the probable basis of the tumorigenic activity of methimazole for the thyroid in experimental animals.

Table 1. Genetic and related effects of methimazole

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Klebsiella pneumoniae, forward mutation	–	NT	5023	Voogd *et al*. (1979)
Chromosomal aberrations, C3H mouse mammary carcinoma cell line *in vitro*	+	NT	365	Kodama *et al*. (1980)
Inhibition of gap-junctional intercellular communication, primary thyrocyte cultures from Sprague-Dawley rats	+	NT	0.1	Asakawa *et al*. (1992)
Sister chromatid exchange, C57BL6 mouse T lymphocytes *in vivo*	+		0.1% in drinking-water, 2–6 weeks	Liu *et al*. (1995)
Chromosomal aberrations, Slc-ICR mouse bone-marrow cells, primary spermatocytes and spermatogonia *in vivo*	–		180 sc × 5	Hashimoto *et al*. (1987)
Micronucleus formation, Slc-ICR mouse bone-marrow cells *in vivo*	–		180 sc × 5	Hashimoto *et al*. (1987)
Dominant lethal mutation, male ICR mice *in vivo*	–		90 sc × 1	Akatsuka *et al*. (1979)

[a] +, positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw per day; sc, subcutaneous

Methimazole was not adequately tested to support a conclusion regarding its classification as a genotoxin or a non-genotoxin. It inhibited gap-junctional intercellular communication in primary rat hepatocytes *in vitro.*

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Methimazole is an anti-thyroid drug, introduced in 1949, which is widely used in the treatment of hyperthyroidism. It has been used as a fattening agent in cattle, but this use has been banned.

5.2 Human carcinogenicity studies

No epidemiological data on use of methimazole and cancer were found. However, two analyses were published of one cohort study conducted in the United Kingdom and the USA of the cancer risk of patients, mainly women, with hyperthyroidism who had been treated with anti-thyroid drugs. The earlier analysis showed more malignant thyroid neoplasms in patients receiving these drugs than in those treated with surgery or ^{131}I, but the excess may have been due to closer surveillance of the patients given drugs owing to more frequent use of thyroidectomy. In the later analysis, patients with hyperthyroidism treated only with anti-thyroid drugs had a modest increase in the risk for death from cancer, due chiefly to oral cancer and cancer of the brain. Neither report provided information on the type, quantity or dates of anti-thyroid drug use.

Two case–control studies of cancer of the thyroid showed no significant association with treatment with anti-thyroid medications.

5.3 Animal carcinogenicity data

Methimazole was tested by oral administration in two limited studies in mice and in one study in rats. In one study in mice, it increased the incidence of thyroid follicular-cell adenomas but only in conjunction with a low-iodine diet. It produced thyroid follicular-cell adenomas and carcinomas in the study in rats.

5.4 Other relevant data

In humans and rodents, methimazole is readily absorbed and rapidly excreted. In rats, glucuronidation is the major metabolic pathway; less is known about its metabolism in humans.

The mode of action of methimazole in the thyroid in experimental animals involves inhibition of thyroid peroxidase, which decreases thyroid hormone production and

increases proliferation by increasing the secretion of thyroid-stimulating hormone. This is the probable basis for the tumorigenic activity of methimazole for the thyroid in experimental animals.

While the overall incidence of malformations in the infants of women given methimazole during pregnancy does not appear to be elevated, there is equivocal evidence for an association with the occurrence of aplasia cutis, a skin defect. Most of the studies in experimental animals focused on the consequences of hypothyroidism subsequent to perinatal or early postnatal exposure of rats to methimazole; effects on adult neurobehavioural and testicular function were found. Neurobehavioural effects have also been reported in mice exposed perinatally to methimazole.

Methimazole has not been adequately tested for its ability to induce gene mutations. It induced chromosomal aberrations in mammalian cells *in vitro*, but the results of studies of its ability to induce chromosomal damage *in vivo* were mainly negative.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of methimazole.

There is *limited evidence* in experimental animals for the carcinogenicity of methimazole.

Overall evaluation

Methimazole is not classifiable as to its carcinogenicity to humans (Group 3).

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