

## METHYLTHIOURACIL

This substance was considered by previous working groups, in 1974 (IARC, 1974) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

### 1. Exposure Data

#### 1.1 Chemical and physical data

##### 1.1.1 Nomenclature

*Chem. Abstr. Serv. Reg. No.:* 56-04-2

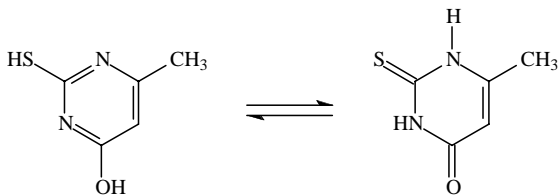
*Deleted CAS Reg. Nos:* 1123-10-0; 31909-18-9; 91795-77-6

*Chem. Abstr. Name:* 2,3-Dihydro-6-methyl-2-thioxo-4(1H)-pyrimidinone

*IUPAC Systematic Name:* 6-Methyl-2-thiouracil

*Synonyms:* 4-Hydroxy-2-mercapto-6-methylpyrimidine; 4-hydroxy-6-methyl-2-mercaptopyrimidine; 2-mercapto-4-methyl-6-hydroxypyrimidine; 2-mercapto-6-methyl-4-pyrimidinol; 2-mercapto-6-methylpyrimidin-4-one; 6-methyl-2-mercapto-uracil; 4-methyl-2-thiouracil; MTU; 2-thio-6-methyluracil; 6-thio-4-methyluracil

##### 1.1.2 Structural and molecular formulae and relative molecular mass



$C_5H_6N_2OS$

Relative molecular mass: 142.18

### 1.1.3 *Chemical and physical properties of the pure substance*

- (a) *Description*: Crystalline solid (Budavari, 2000)
- (b) *Boiling-point*: Sublimes (Lide & Milne, 1996)
- (c) *Melting-point*: 330 °C (sublimes) (Lide & Milne, 1996)
- (d) *Spectroscopy data*: Infrared [prism (8429), grating (24088)], ultraviolet (2236), nuclear magnetic resonance [proton (11278), C-13 (1639)] and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).
- (e) *Solubility*: Insoluble in water; slightly soluble in benzene, diethyl ether, ethanol and methanol (Lide & Milne, 1996)

### 1.1.4 *Technical products and impurities*

Trade names for methylthiouracil include Alkiron, Antibason, Basecil, Basethyrin, Metacil, Methacil, Methiacil, Methicil, Methiocil, Muracil, Prostrumyl, Strumacil, Thimecil, Thiothymin, Thyreonorm, Thyreostat, Thyreostat I, Tiomeracil and Tiorale M.

### 1.1.5 *Analysis*

Methods have been reported for the analysis of methylthiouracil in biological fluids (blood, milk, serum, urine), tissues, dried animal feed and feed additives. 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 and electrochemical detection and gas chromatography with mass spectrometry (Saldaña Monllor *et al.*, 1980; Moretti *et al.*, 1986; Hooijerink & De Ruig, 1987; Moretti *et al.*, 1988; Centrich Escarpenter & Rubio Hernández, 1990; De Brabander *et al.*, 1992; Moretti *et al.*, 1993; Batjoens *et al.*, 1996; Krivánková *et al.*, 1996; Blanchflower *et al.*, 1997; Le Bizec *et al.*, 1997; Yu *et al.*, 1997; Buick *et al.*, 1998; Vargas *et al.*, 1998; Esteve-Romero *et al.*, 1999).

## 1.2 **Production**

Methylthiouracil can be made by condensation of ethyl acetoacetate with thiourea (IARC, 1974)

Information available in 2000 indicated that methylthiouracil was manufactured by two companies each in China and Germany and one company each in Austria, Italy and Japan (CIS Information Services, 2000a; Herbrand, 2000).

Information available in 2000 indicated that methylthiouracil was used in the formulation of pharmaceutical drugs by one company in Poland (CIS Information Services, 2000b).

### 1.3 Use

Methylthiouracil was introduced in the mid-1940s, at the same time as propylthiouracil, as a thionamide anti-thyroid drug for the treatment of hyperthyroidism. The usual dose is 200 mg/day in two to four equally spaced doses. Methylthiouracil is no longer in clinical use in most countries, although it may be used to a limited degree in some eastern European countries. It has not been registered for human use since 1958 in Sweden, 1986 in the United Kingdom and 1988 in the Netherlands (Medical Products Agency, 2000; Medicines Control Agency, 2000; Medicines Evaluation Board Agency, 2000). A MEDLINE search revealed no references to use of methylthiouracil since 1987 (Junik *et al.*, 1987). This may be related to the higher rate of adverse reactions than with propylthiouracil or methimazole (see monographs in this volume) (Van der Laan & Storrie, 1955).

### 1.4 Occurrence

#### 1.4.1 Occupational exposure

No data were available to the Working Group.

#### 1.4.2 Environmental occurrence

No data were available to the Working Group.

### 1.5 Regulations and guidelines

Methylthiouracil is listed in the current pharmacopoeias of Austria, Poland and Switzerland. It was previously listed in the pharmacopoeias of the former East Germany, Italy, Japan (1976), the United Kingdom (1973) and the USA (XXI) (Royal Pharmaceutical Society of Great Britain, 2000; Swiss Pharmaceutical Society, 2000). It was also formerly listed in the International Pharmacopoeia (II).

## 2. Studies of Cancer in Humans

No information was available specifically on methylthiouracil.

### 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  $^{131}\text{I}$  (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  $^{131}\text{I}$  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  $^{131}\text{I}$  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  $^{131}\text{I}$  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  $^{131}\text{I}$  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 separately for patients treated only with drugs and 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

Methylthiouracil was evaluated in a previous monograph (IARC, 1974). Although there have been several new studies on the carcinogenicity of methylthiouracil in animals, no conventional bioassays have been reported. The summaries of the most relevant studies from the previous monograph are either repeated here or the studies are analysed in greater depth. Studies on the carcinogenicity of anti-thyroid chemicals, including methylthiouracil, in experimental animals have been reviewed (Doniach, 1970; Christov & Raichev, 1972a).

#### 3.1 Oral administration

*Mouse:* In a study published since the previous evaluation, groups of 94 male and 82 female C3H/FIB mice, 2 months of age, were given methylthiouracil [purity not specified] in their drinking-water at a concentration of 0 or 1000 mg/L in conjunction with an iodine-rich diet (9–10 mg/kg). A group of 236 male and 239 female mice served as untreated controls on an iodine-rich diet. Another group of 42 males and 53 females of the same strain and age received methylthiouracil mixed into pelleted diet at a concentration of 2000 mg/kg, which was increased to 5000 mg/kg of diet when they were 4 months of age, in conjunction with an iodine-poor diet (90 µg/kg). Groups of 50 males and 50 females served as untreated controls on iodine-poor diet. Groups of animals were killed after 6–22 months of treatment. Methylthiouracil caused a statistically significant increase ( $p < 0.01$ ) in the incidence of thyroid adenomas in mice on the iodine-poor diet (23/75, including 13/75 with pulmonary metastases). In contrast, the incidences of thyroid adenoma were 1/150 in control mice on the iodine-poor diet, 0/249 in control mice on the iodine-rich diet and 2/167 in methylthiouracil-treated mice on the iodine-rich diet. Methylthiouracil also produced hepatomas in 28/75 mice on the iodine-poor diet ( $p < 0.01$ ), in 6/167 mice on the iodine-rich diet, in 2/150 control mice on the iodine-poor diet and in 6/249 control mice on the iodine-rich diet. All of these incidences refer to pooled males and females (Jemec, 1977).

*Rat:* Groups of female Long-Evans rats, approximately 9 months of age, were given methylthiouracil [route not specified clearly but presumed to be dietary] at a dose of 0 (31 rats at start) or 2.5 mg/rat per day (34 rats at start) in combination with a low-

iodine diet (average, 100–150 µg/kg of diet) for 24–33 months. Administration of methylthiouracil resulted in thyroid hyperplasia in 22/24 rats, ‘nodular thyroid changes’ in 15/24 rats and thyroid carcinoma in 8/24 rats examined. In the group receiving the low-iodine diet only, 1/31 had thyroid hyperplasia, 3/31 had nodular changes and 0/31 had thyroid carcinoma (Field *et al.*, 1959). [The Working Group considered the nodular changes to be adenomas.]

In a study published since the previous evaluation, two groups of inbred Wistar/FIB rats (39 and 57 animals at start), 2 months of age, were given methylthiouracil [purity not specified] in their drinking-water at a concentration of 0 (control) or 0.1% [length of exposure not specified]. A third group (43 rats at start) was hypophysectomized, given methylthiouracil (0.1%) 5–6 days after the operation and killed 7–8 months later. The author reported that the average age at death did not differ significantly in the three groups. Thyroid tumours occurred in 16/57 intact rats given methylthiouracil, 0/39 of the controls and 0/32 hypophysectomized rats receiving methylthiouracil. Of the 16 tumour-bearing rats given methylthiouracil only, nine had thyroid adenomas and seven had carcinomas metastasizing to the lungs. As part of a second experiment, groups of Wistar/FIB rats [initial numbers and sex not specified], 2 months of age, were given methylthiouracil [purity not specified] in the drinking-water at a concentration of 0 (control) or 0.25% for 2 years. Methylthiouracil induced thyroid adenomas in 11/30 rats (five with pulmonary nodules), whereas none were seen in 33 controls (Jemec, 1980).

In another study published since the previous evaluation, groups of white random-bred rats, 3 months of age, were given methylthiouracil [purity not specified] in the drinking-water at a concentration of 0 or 0.1% until natural death or were killed when moribund. Methylthiouracil produced thyroid tumours in 39/58 treated rats (38 adenomas, one carcinoma;  $p < 0.01$ ) and produced thyroid adenomas in 3/100 controls (Alexandrov *et al.*, 1989).

*Hamster:* Groups of hamsters, 3 months of age, were given methylthiouracil [purity not specified] in the drinking-water at a concentration of 0 (control) or 0.2%. Between four and 12 animals in each group were killed at regular intervals after 2–12 months of exposure. The first thyroid adenoma was recorded after 5 months of treatment with methylthiouracil; the total incidence of animals with thyroid adenomas by the end of the experiment was 20/77 treated hamsters and 0/37 controls (Christov & Raichev, 1972b).

### 3.2 Administration with known carcinogens

*Rat:* Groups of Debrecen or CB albino rats of each sex [initial numbers unspecified], 2.5–4 months of age, were given 2-acetylaminofluorene intragastrically at a dose of 2.5 mg/rat three times a week for 6 weeks and methylthiouracil [purity not specified] in the drinking-water at a concentration of 0.01% for a total experimental period of 71 weeks. Combined exposure to 2-acetylaminofluorene, methylthiouracil and a low-iodine diet produced thyroid adenomas in 100% of the rats that lived for 5 months or

longer [number not stated], compared with 0/30 rats treated with 2-acetylaminofluorene alone and 1/25 rats treated with methylthiouracil alone (Lapis & Vekerdi, 1962).

In a study published since the previous evaluation, 75 female Wistar rats weighing 150 g [age not specified] were given a single oral dose of 40 mg/kg bw *N*-methyl-*N*-nitrosourea (MNU) on 3 consecutive days followed 4 weeks later by methylthiouracil [purity not specified] in the drinking-water at a concentration of 0.1% up to week 60 of the experiment. Thyroid tumours were observed from week 16 and carcinomas from week 24. After 30 weeks, 13 rats had tumours with metastases to the lungs (Schäffer & Müller, 1980). [The Working Group noted that the numbers of rats sampled at various times were not given, nor was the incidence, but the latter was inferred to be 100%.]

In a multigeneration study published since the previous evaluation, groups of white random-bred female rats [initial numbers and age not specified] received an intraperitoneal injection of MNU at 20 mg/kg bw in 0.9% saline on day 21 of gestation. Groups of rats of the F<sub>1</sub> generation received either no further treatment or methylthiouracil in their drinking-water at a concentration of 0.1% (about 100 mg/kg bw per day) for life. Two additional groups of rats with no transplacental exposure to MNU received either methylthiouracil alone as above or no treatment (control group). Methylthiouracil caused a statistically significant increase ( $p < 0.01$ ) in the incidence of MNU-induced thyroid tumours, from 4/100 with MNU alone to 33/43 with MNU plus methylthiouracil, but decreased ( $p < 0.01$ ) the incidence of MNU-induced kidney and nervous system tumours. The incidences of thyroid tumours in rats given methylthiouracil are reported in section 3.1.2 (Alexandrov *et al.*, 1989).

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

### **4.1 Absorption, distribution, metabolism and excretion**

#### *4.1.1 Humans*

No data were available to the Working Group.

#### *4.1.2 Experimental systems*

After intravenous injection of a single dose of 5 mg methylthiouracil, 84–90% of the dose could be recovered from the carcasses of animals killed after 1 min and 55–60% from the carcasses of animals killed after 3 h. At 3 h, the concentration of methylthiouracil in the thyroid was approximately 1 mg/g of tissue (Williams & Kay, 1947).

Methylthiouracil crossed the placental barrier and was excreted in the milk of lactating rats (Napalkov & Alexandrov, 1968).

After male Sprague-Dawley rats were given an intraperitoneal injection of [<sup>35</sup>S]methylthiouracil in alkaline saline (pH 8.0), accumulation of radiolabel was observed in the thyroid, with a thyroid:plasma ratio of 43 (Marchant *et al.*, 1972).

## **4.2 Toxic effects**

### **4.2.1 Humans**

Use of methylthiouracil is associated with a high frequency of agranulocytosis (Westwick *et al.*, 1972). Use of this drug by a 21-year-old woman led to a bullous haemorrhagic rash (Cox *et al.*, 1985).

### **4.2.2 Experimental systems**

Methylthiouracil (0.03%) given in the drinking-water to male Wistar rats had increased the plasma concentrations of thyroid-stimulating hormone by 1 week after the start of the treatment; however, the plasma concentrations of triiodothyronine and thyroxine were markedly decreased by 2 weeks (Tohei *et al.*, 1997).

Male Wistar/Holtzman rats given an intraperitoneal injection of 40 mg of methylthiouracil showed acute increases in the secretion of thyroid-stimulating hormone and interference with the recycling of iodide (Onaya *et al.*, 1973).

Male and female C57BL mice were given diets containing methylthiouracil at a concentration of 0.3 or 0.5% *ad libitum* for 2 weeks. Mice with hypothalamic lesions had decreased goitre development (Moll *et al.*, 1969).

Methylthiouracil given at a concentration of 0.1% in the drinking-water to male Wistar rats for 3 weeks led to disappearance of thyroid peroxidase activity from the follicular cells, measured by histochemistry; however, the activity reappeared after prolonged treatment for 6 months (Christov & Stoichkova, 1977).

Wistar rats treated with 0.1% methylthiouracil in their drinking-water had a fourfold increase in thyroid weights within 3 months and a 10-fold increase within 15 months. The mitotic index had increased by 10–15-fold in hyperplastic and malignant cells at 9 months (Christov, 1985).

## **4.3 Reproductive and developmental effects**

No data were available to the Working Group.

## **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)

Methylthiouracil was not mutagenic to *Salmonella typhimurium* in an assay with preincubation when tested with or without metabolic activation. It induced somatic recombination in eye cells in all three strains of *Drosophila melanogaster* tested when administered continuously in feed to larvae.

Methylthiouracil did not induce micronucleus formation in male mice after intraperitoneal injection or oral gavage [details not provided]. When the drug was administered orally in two doses to pregnant mice, it appeared to increase the frequency of micronucleated polychromatic erythrocytes in the fetuses, but no micronucleus formation was seen in maternal bone-marrow cells. However, it is not clear that the same or similar cell populations were observed in the control and treated groups (the percentages of nucleated cells were quite different), and there was no significant increase in the number of micronucleated cells at doses of 5–100 mg/kg bw.

## 4.6 Mechanistic considerations

Inadequate data were available on the genotoxicity of methylthiouracil.

Methylthiouracil belongs to a class of drugs used in the treatment of hyperthyroidism. The mode of action is inhibition of thyroid peroxidase, which decreases thyroid hormone production and increases follicular-cell proliferation by increasing the secretion of thyroid-stimulating hormone. This is assumed to be the basis of the tumorigenic activity of methylthiouracil in the thyroid in experimental animals; however, the lack of adequate data limits the confidence with which conclusions can be drawn.

The lack of adequate data on genotoxicity for methylthiouracil precludes a conclusion regarding the mechanism of carcinogenesis.

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Methylthiouracil is a thionamide anti-thyroid drug, introduced in the 1940s, which has been used in the treatment of hyperthyroidism. Little is known about its current use.

**Table 1. Genetic and related effects of methylthiouracil**

Test system	Result <sup>a</sup>		Dose <sup>b</sup> (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
<i>Salmonella typhimurium</i> TA100, TA1535, TA98, TA97, reverse mutation	–	–	10 000 µg/plate	Zeiger <i>et al.</i> (1992)
<i>Drosophila melanogaster</i> , somatic recombination, <i>w/w</i> locus	+		71 µg/mL in feed	Rodriguez-Arnaiz (1998)
Micronucleus formation, peripheral blood cells of male CD-1 mice <i>in vivo</i>	–		2000 ip × 2 or po × 1	Morita <i>et al.</i> (1997)
Micronucleus formation, blood cells of fetal AG <sub>2</sub> mice, transplacental exposure <i>in vivo</i>	(+)		5 po × 2	Ioan (1980)
Micronucleus formation, bone-marrow cells of pregnant AG <sub>2</sub> mice <i>in vivo</i>	–		100 po × 2	Ioan (1980)

<sup>a</sup> +, positive; –, negative; (+), weak positive

<sup>b</sup> LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal injection; po, oral gavage

## 5.2 Human carcinogenicity studies

No epidemiological data on use of methylthiouracil 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  $^{131}\text{I}$ , 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

Although no conventional bioassay of carcinogenicity in rodents has been reported, methylthiouracil has produced tumours in three species of laboratory rodents after oral administration. In two studies in mice, multiple studies in rats and one study in hamsters, methylthiouracil produced thyroid follicular-cell adenomas and/or carcinomas after oral administration. In initiation-promotion studies with the known carcinogens 2-acetylaminofluorene and *N*-methyl-*N*-nitrosourea, methylthiouracil increased the incidence of thyroid follicular-cell tumours.

## 5.4 Other relevant data

Little is known about the disposition of methylthiouracil in humans. In rats, methylthiouracil was found to accumulate in the thyroid. The compound crosses the placental barrier and is transferred rapidly across the placenta throughout gestation.

Human exposure to methylthiouracil is associated with a high frequency of agranulocytosis.

The available data on the mechanism of action of methylthiouracil in experimental animals is limited, but inhibition of thyroid peroxidase and increased secretion of thyroid-stimulating hormone may be the basis of its tumorigenic activity in the thyroid.

No data were available on reproductive or developmental effects of methylthiouracil.

Methylthiouracil was not mutagenic in single studies of reverse mutation in bacteria and bone-marrow micronucleus formation in rodents. It induced chromosomal recombination in somatic cells of insects. It gave an inconclusive response in a test for micronucleus formation in fetal mouse blood cells.

## 5.5 Evaluation

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

There is *sufficient evidence* in experimental animals for the carcinogenicity of methylthiouracil.

## Overall evaluation

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

## 6. References

- Alexandrov, V.A., Popovich, I.G., Anisimov, V.N. & Napalkov, N.P. (1989) Influence of hormonal disturbances on transplacental and multigeneration carcinogenesis in rats. In: Napalkov, N.P., Rice, J.M., Tomatis, L. & Yamasaki, H., eds, *Perinatal and Multigeneration Carcinogenesis* (IARC Scientific Publications No. 96), Lyon, IARC Press, pp. 35–49
- Batjoens, P., De Brabander, H.F. & De Wasch, K. (1996) Rapid and high-performance analysis of thyreostatic drug residues in urine using gas chromatography–mass spectrometry. *J. Chromatogr.*, **A750**, 127–132
- Blanchflower, W.J., Hughes, P.J., Cannavan, A., McCoy, M.A. & Kennedy, D.G. (1997) Determination of thyreostats in thyroid and urine using high-performance liquid chromatography–atmospheric pressure chemical ionization mass spectrometry. *Analyst*, **122**, 967–972
- Budavari, S., ed. (2000) *The Merck Index*, 12th Ed., Version 12:3, Whitehouse Station, NJ, Merck & Co. & Boca Raton, FL, Chapman & Hall/CRC [CD-ROM]
- Buick, R.K., Barry, C., Traynor, I.M., McCaughey, W.J. & Elliott, C.T. (1998) Determination of thyreostat residues from bovine matrices using high-performance liquid chromatography. *J. Chromatogr. B. Biomed. Sci. Appl.*, **720**, 71–79
- Centrich Escarpenter, F. & Rubio Hernández, D. (1990) [Analysis of thyrostatics in the thyroid glands by thin layer chromatography and HPLC-UV.] *An. Bromatol.*, **42**, 337–344 (in Spanish)
- Christov, K. (1985) Cell population kinetics and DNA content during thyroid carcinogenesis. *Cell Tissue Kinet.*, **18**, 119–131
- Christov, K. & Raichev, R. (1972a) Experimental thyroid carcinogenesis. *Curr. Top. Pathol.*, **56**, 79–114
- Christov, K. & Raichev, J.R. (1972b) Thyroid carcinogenesis in hamsters after treatment with <sup>131</sup>-iodine and methylthiouracil. *Z. Krebsforsch.*, **77**, 171–179
- Christov, K. & Stoichkova, N. (1977) Cytochemical localization of peroxidase activity in normal, proliferating and neoplastic thyroid tissues of rats. An ultrastructural study. *Acta histochem.*, **58**, 275–289
- CIS Information Services (2000a) *Directory of World Chemical Producers (Version 2000.1)*, Dallas, TX [CD-ROM]

- CIS Information Services (2000b) *Worldwide Bulk Drug Users Directory (Version 2000)*, Dallas, TX [CD-ROM]
- Cox, N.H., Dunn, L.K. & Williams, J. (1985) Cutaneous vasculitis associated with long-term thiouracil therapy. *Clin. exp. Dermatol.*, **10**, 292–295
- De Brabander, H.F., Batjoens, P. & Van Hoof, J. (1992) Determination of thyreostatic drugs by HPTLC with confirmation by GC-MS. *J. planar Chromatogr. Mod. TLC*, **5**, 124–130
- Dobyns, B.M., Sheline, G.E., Workman, J.B., Tompkins, E.A., McConahey, W.M. & Becker, D.V. (1974) Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: A report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. *J. clin. Endocrinol. Metab.*, **38**, 976–998
- Doniach, I. (1970) Experimental thyroid tumours. In: Smithers, D., ed., *Neoplastic Disease at Various Sites*, Vol. 6, *Tumours of the Thyroid Gland*, Edinburgh, E. & S. Livingstone, pp. 73–99
- Esteve-Romero, J., Escrig-Tena, I., Simó-Alfonso, E.F. & Ramis-Ramos, G. (1999) Determination of thyreostatics in animal feed by micellar electrokinetic chromatography. *Analyst*, **124**, 125–128
- Field, J.B., McCammon, C.J., Valentine, R.J., Bernick, S., Orr, C. & Starr, P. (1959) Failure of radioiodine to induce thyroid cancer in the rat. *Cancer Res.*, **19**, 870–873
- Hallquist, A., Hardell, L., Degerman, A. & Boquist, L. (1994) Thyroid cancer: Reproductive factors, previous diseases, drug intake, family history and diet. A case–control study. *Eur. J. Cancer Prev.*, **3**, 481–488
- Herbrand, K.G. (2000) *Pharmaceutical Specialties for the Treatment of Thyroid Diseases (Hyperthyroidism)*, Gengenbach, Germany [www.herbrand-pharma.de]
- Hooijerink, H. & De Ruig, W.G. (1987) Determination of thyreostatics in meat by reversed-phase liquid chromatography with ultraviolet and electrochemical detection. *J. Chromatogr.*, **394**, 403–407
- IARC (1974) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 7, *Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals*, Lyon, IARC Press, pp. 53–65
- IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42*, Lyon, IARC Press, p. 66
- Ioan, D. (1980) The mutagenic effect of carbimazol and methylthiouracil detected by the transplacental micronucleus test. *Rev. Roum. Med. Endocrinol.*, **18**, 247–250
- Jemec, B. (1977) Studies of the tumorigenic effect of two goitrogens. *Cancer*, **40**, 2188–2202
- Jemec, B. (1980) Studies of the goitrogenic and tumorigenic effect of two goitrogens in combination with hypophysectomy or thyroid hormone treatment. *Cancer*, **45**, 2138–2148
- Junik, R., Lacka, K., Sowinski, J., Horst-Sikorska, W. & Gembicki, M. (1987) [Antithyroid antibodies and thyroglobulin in the serum of patients with hyperthyroidism treated with methylthiouracil.] *Polski Togodnik Lek.*, **42**, 1120–1123 (in Polish)
- Krivánková, L., Krásenský, S. & Bocek, P. (1996) Application of capillary zone electrophoresis for analysis of thyreostatics. *Electrophoresis*, **17**, 1959–1963
- Lapis, K. & Vekerdi, L. (1962) Simultaneous histological, autoradiographic and biochemical examination of experimentally induced thyroid tumour. *Acta morphol. sci. hung.*, **11**, 267–283

- Le Bizec, B., Monteau, F., Maume, D., Montrade, M.-P., Gade, C. & Andre, F. (1997) Detection and identification of thyreostats in the thyroid gland by gas chromatography–mass spectrometry. *Anal. chim. Acta*, **340**, 201–208
- Lide, D.R. & Milne, G.W.A. (1996) *Properties of Organic Compounds*, Version 5.0, Boca Raton, FL, CRC Press [CD-ROM]
- Marchant, B., Alexander, W.D., Lazarus, J.H., Lees, J. & Clark, D.H. (1972) The accumulation of <sup>35</sup>S-antithyroid drugs by the thyroid gland. *J. clin. Endocrinol. Metab.*, **34**, 847–851
- Medical Products Agency (2000) Uppsala
- Medicines Control Agency (2000) London
- Medicines Evaluation Board Agency (2000) The Hague
- Moll, J., Martens, E. & Jansen, H.G. (1969) Development of goitre after methylthiouracil treatment of mice with hypothalamic lesions. *J. Endocrinol.*, **45**, 483–488
- Moretti, G., Amici, M. & Cammarata, P. (1986) [Determination of methylthiouracil and analogous thyrostatics in animal tissues by HPTLC after solid-phase purification.] *Riv. Soc. ital. Sci. aliment.*, **15**, 35–39 (in Italian)
- Moretti, G., Amici, M., Cammarata, P. & Fracassi, F. (1988) Identification of thyrostatic drug residues in animal thyroids by high-performance thin-layer chromatography and fluorescence reaction detection. *J. Chromatogr.*, **442**, 459–463
- Moretti, G., Betto, R., Cammarata, P., Fracassi, F., Giambenedetti, M. & Borghese, A. (1993) Determination of thyreostatic residues in cattle plasma by high-performance liquid chromatography with ultraviolet detection. *J. Chromatogr.*, **616**, 291–296
- Morita, T., Asano, N., Awogi, T., Sasaki, Y.F., Sato, S., Shimada, H., Sutou, S., Suzuki, T., Wakata, A., Sofuni, T. & Hayashi, M. (1997) Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (Groups 1, 2A and 2B). The summary report of the 6th collaborative study by CSGMT/JEMS.MMS. *Mutat. Res.*, **389**, 3–122
- Napalkov, N.P. & Alexandrov, V.A. (1968) On the effects of blastomogenic substances on the organism during embryogenesis. *Z. Krebsforsch.*, **71**, 32–50
- Onaya, T., Yamada, T. & Halmi, N.S. (1973) Intrathyroidal recycling of iodide in the rat: Effects of goitrogens. *Proc. Soc. exp. Biol. Med.*, **143**, 181–184
- Rodriguez-Arnaiz, R. (1998) Biotransformation of several structurally related 2B compounds to reactive metabolites in the somatic *w/w*<sup>+</sup> assay of *Drosophila melanogaster*. *Environ. mol. Mutag.*, **31**, 390–401
- Ron, E., Kleinerman, R.A., Boice, J.D., Jr, LiVolsi, V.A., Flannery, J.T. & Fraumeni, J.F., Jr (1987) A population-based case–control study of thyroid cancer. *J. natl Cancer Inst.*, **79**, 1–12
- Ron, E., Doody, M.M., Becker, D.V., Brill, A.B., Curtis, R.E., Goldman, M.B., Harris, B.S.H., Hoffman, D.A., McConahey, W.M., Maxon, H.R., Preston-Martin, S., Warshauer, E., Wong, F.L. & Boice, J.D., Jr for the Cooperative Thyrotoxicosis Therapy Follow-up Study Group (1998) Cancer mortality following treatment for adult hyperthyroidism. *J. Am. med. Assoc.*, **280**, 347–355
- Royal Pharmaceutical Society of Great Britain (2000) *Martindale, The Extra Pharmacopoeia*, 13th Ed., London, The Pharmaceutical Press [MicroMedex Online]
- Sadtler Research Laboratories (1980) *Sadtler Standard Spectra, 1980 Cumulative Molecular Formula Index*, Philadelphia, PA, p. 61

- Saldaña Monllor, L., Carbonell Martín, G. & Alonso Fuente, C. (1980) [*Thin-layer Chromatographic Separation and Identification of 2-Thiouracil, 4(6)-Methyl-2-thiouracil and 6(4)-Propyl-2-thiouracil in Feed Additives and Biological Materials by Thin-layer Chromatography.*], Madrid, Instituto Nacional de Investigaciones Agrarias (in Spanish)
- Schäffer, R. & Müller, H.-A. (1980) On the development of metastasizing tumors of the rat thyroid gland after combined administration of nitrosomethylurea and methylthiouracil. *J. Cancer Res. clin. Oncol.*, **96**, 281–285
- Swiss Pharmaceutical Society, ed. (2000) *Index Nominum, International Drug Directory*, 16th Ed., Stuttgart, Medpharm Scientific Publishers [MicroMedex Online]
- Tohei, A., Akai, M., Tomabechi, T., Mamada, M. & Taya, K. (1997) Adrenal and gonadal function in hypothyroid adult male rats. *J. Endocrinol.*, **152**, 147–154
- Van der Laan, W.P. & Storrie, V.M. (1955) A survey of factors controlling thyroid function, with especial reference to newer views on antithyroid substances. *Pharm. Rev.*, **7**, 301–334
- Vargas, G., Havel, J. & Frgalová, K. (1998) Capillary zone electrophoresis determination of thyreostatic drugs in urine. *J. capillary Electrophor.*, **5**, 9–12
- Westwick, W.J., Allsop, J. & Watts, R.W. (1972) A study of the effect of some drugs which cause agranulocytosis on the biosynthesis of pyrimidines in human granulocytes. *Biochem. Pharmacol.*, **15**, 1955–1966
- Williams, R.H. & Kay, G.A. (1947) Thiouracils and thioureas: Comparisons of the absorption, distribution, destruction and excretion. *Arch. intern. Med.*, **80**, 37–52
- Yu, G.Y.F., Murby, E.J. & Wells, R.J. (1997) Gas chromatographic determination of residues of thyreostatic drugs in bovine muscle tissue using combined resin mediated methylation and extraction. *J. Chromatogr. B. Biomed. Sci. Appl.*, **703**, 159–166
- Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. & Mortelmans, K. (1992) *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. mol. Mutag.*, **19** (Suppl. 21), 2–141