THIOUREA

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.

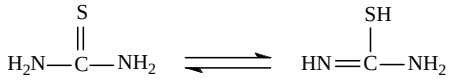
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 62-56-6
Chem. Abstr. Name: Thiourea
IUPAC Systematic Name: Thiourea
Synonyms: Isothiourea; pseudothiourea; thiocarbamide; 2-thiopseudourea; β-thiopseudourea; 2-thiourea; THU

1.1.2 *Structural and molecular formulae and relative molecular mass*



CH_4N_2S Relative molecular mass: 76.12

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White solid which crystallizes in a rhombic bipyramidal structure (Mertschenk & Beck, 1995; Lide & Milne, 1996)
(*b*) *Melting-point*: 182 °C (Lide & Milne, 1996)
(*c*) *Spectroscopy data*: Infrared [prism (3962), grating (8315)], ultraviolet (3292), nuclear magnetic resonance [proton (12880), C-13 (6809)] and mass spectral

data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).

(*d*) *Solubility*: Soluble in water (140 g/L at 20 °C) and ethanol; insoluble in diethyl ether (Mertschenk & Beck, 1995; Lide & Milne, 1996)

1.1.4 *Technical products and impurities*

Thiourea is commercially available in Germany with the following typical specifications: purity, ≥ 99.0%; water, ≤ 0.30%; ash, ≤ 0.10%; thiocyanate (rhodanide), ≤ 0.15%; other nitrogen-containing compounds, ≤ 0.5%; and iron, ≤ 10 mg/kg. Special grades with higher purity are also available (Mertschenk & Beck, 1995).

Trade names for thiourea include TsizP 34.

1.1.5 *Analysis*

Methods for the analysis of thiourea in citrus fruit juices and peels, urine, wine, wastewater, magnetic film plating solutions, copper electrolyte solutions and zinc electroplating solutions have been reported. The methods include colorimetry, ultraviolet spectrophotometry, direct ultraviolet reflectance spectrometry, atmospheric-pressure chemical ionization mass spectrometry, gas chromatography, high-performance liquid chromatography (HPLC) with ultraviolet detection, reversed-phase HPLC with ultraviolet detection, periodate titration, potentiometric titration with an ion-selective electrode, anodic and cathodic stripping voltammetry, cathodic polarization potentiometry, chemiluminescence spectroscopy, flow-injection amperometry, flow-injection fluorimetry, micellar electrokinetic capillary chromatography and atomic absorption spectrometry (Mandrou *et al*., 1977a,b; Toyoda *et al*., 1979; Akintonwa, 1985; Bian, 1985; Grigorova & Wright, 1986; Kiryushov *et al*., 1986; Zejnilovic & Jovanovic, 1986; Xu *et al*., 1987; Sastry *et al*., 1988; Abdalla & Al-Swaidan, 1989; Berestetskii & Tulyupa, 1989; Zhou *et al*., 1990; Komljenovic & Radic, 1991; Budnikov *et al*., 1992; Chemezova & Khlynova, 1992; Kiryushov, 1992; Lebedev *et al*., 1992; Yao *et al*., 1992; He *et al*., 1994; Lee *et al*., 1994; Pérez-Ruiz *et al*., 1995; Shao, 1995; Wang, 1996a,b; Anisimova *et al*., 1997; Huang *et al*., 1997; Raffaelli *et al*., 1997; Duan *et al*., 1998; Kato *et al*., 1998; Xu & Tang, 1998; AOAC International, 1999; He *et al*., 1999; Hida *et al*., 1999).

1.2 Production

Thiourea was first prepared by thermal rearrangement of ammonium thiocyanate at approximately 150 °C. As this is an equilibrium reaction and separation of the two substances is quite difficult, better methods of preparation were investigated. Production of thiourea is now carried out by treating technical-grade calcium cyanamide with hydrogen sulfide or one of its precursors, e.g., ammonium sulfide or calcium hydrogen

sulfide. In Germany, thiourea is produced in a closed system by reaction of calcium cyanamide with hydrogen sulfide. The quantity of thiourea produced worldwide in 1995 was estimated to be 10 000 t/year (Mertschenk & Beck, 1995; Budavari, 2000).

Information available in 2000 indicated that thiourea was manufactured by 44 companies in China, three companies each in Japan and Mexico, two companies each in Germany and Italy and one company each in India, Poland, the Russian Federation, Spain, Taiwan, the Ukraine and Uzbekistan (CIS Information Services, 2000a).

Information available in 2000 indicated that thiourea was used in the formulation of pharmaceuticals by six companies in Italy, two companies in Switzerland and one company in Germany (CIS Information Services, 2000b).

1.3 Use

Thiourea has a wide range of uses, such as for producing and modifying textile and dyeing auxiliaries, in the production and modification of synthetic resins, in image reproduction, in the production of pharmaceuticals (sulfathiazoles, thiouracils, tetramisole and cephalosporins), in the production of industrial cleaning agents (e.g., for photographic tanks and metal surfaces in general), for engraving metal surfaces, as an isomerization catalyst in the conversion of maleic to fumaric acid, in copper refining electrolysis, in electroplating (e.g., of copper) and as an antioxidant (e.g., in biochemistry). Other uses are as a vulcanization accelerator, an additive for slurry explosives, as a viscosity stabilizer for polymer solutions (e.g., in drilling muds) and as a mobility buffer in petroleum extraction. The removal of mercury from wastewater by chlorine–alkali electrolysis and gold and silver extraction from minerals are also uses of economic importance (Mertschenk & Beck, 1995; Budavari, 2000). Thiourea was investigated as an anti-thyroid drug in the 1940s (Winkler *et al.*, 1947). It is used only as an excipient in drugs in Italy and in Portugal (Instituto Nacional de Farmacia e do Medicamento, 2000; Ministry of Health, 2000).

Thiourea is used in four main ways: as an intermediate in the production of thiourea dioxide for wool and textile processing (30%), in ore leaching (25%), in diazo papers (15%) and as a catalyst in fumaric acid synthesis (10%); the remainder has smaller areas of use (Mertschenk & Beck, 1995). Thiourea is registered as a veterinary agent in Ireland and Sweden.

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 38 000 workers in the USA were potentially exposed to thiourea. Occupational exposure occurred, e.g., in the metal product industry (7900 exposed), chemical industry (6000), machinery except electrical

industry (3500), electric and electronic equipment production (3500), instrument production (3500), health services (3100), transportation equipment (2600), business services (1800) and lumber and wood product mills (1000). The most commonly exposed occupational group was that of machine operators (8000 workers). According to the Finnish Register of Employees Exposed to Carcinogens, about 100 laboratory workers, nurses or surface treatment workers were exposed to thiourea in Finland in 1997 (Savela *et al*., 1999).

1.4.2 *Environmental occurrence*

No data were available to the Working Group.

1.5 Regulations and guidelines

Thiourea is classified as a suspected carcinogen in Germany and the European Union and as a carcinogen in Finland (1993), France (1993), Japan (1999) and Sweden (1993); the Netherlands recommended in 1999 an occupational exposure limit of 0.5 mg/m^3 with a skin notation; and the Russian Federation in 1993 imposed a short-term exposure limit of 0.3 mg/m^3 (Mertschenk & Beck, 1995; American Conference of Governmental Industrial Hygienists, 2000; Deutsche Forschungsgemeinschaft, 2000).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Since the first evaluation of thiourea (IARC, 1974), there have been a few studies on its carcinogenicity in animals, but none representing a conventional carcinogenicity bioassay meeting present-day standards. A selection of the most relevant studies from the previous monograph were therefore summarized or re-analysed in greater depth. Studies on the carcinogenicity of anti-thyroid chemicals, including thiourea, in experimental animals have been reviewed (Paynter *et al*., 1988).

3.1 Oral administration

Mouse: Of four studies in several strains of mice conducted prior to 1952 in which various concentrations of thiourea were administered in the diet or drinking-water for various times ranging from 7 months to life, none reported an increased incidence of

thyroid tumours; however, some reported thyroid hyperplasia (Gorbman, 1947; Dalton *et al*., 1948; Vasquez-Lopez, 1949; Casas & Koppisch, 1952). One representative study is described below.

Groups of 31 strain A, 43 C57 and 17 strain I mice [sex unspecified], 1–3 months of age, were fed a diet containing thiourea [purity not specified] at a concentration of 2% for various periods up to 81 weeks [the numbers of animals examined at each time were not given]. The survival rate at necropsy was 58% for strain A, 66% for C57 and 71% for strain I mice. The author reported that thyroid hyperplasia was seen from 40 days of treatment, developing into cystic or nodular lesions from 150 days. Seven strain A mice out of 22 that lived longer than 300 days of treatment had nodules of 'thyroid-like tissue' in the lungs. [It was not clear whether all of these mice were fed thiourea, as the study also included thiouracil-treated groups.] The author considered the thyroid and pulmonary lesions to be non-malignant (Gorbman, 1947).

Rat: Groups of 10 male and 10 female albino rats (New Zealand strain of *Rattus norvegicus*) and 10 male Wistar rats, 8 weeks of age, were given drinking-water containing thiourea [purity not specified] at a concentration of 0.25% for up to 23.5 months. The survival rate for 12 months or longer was 90% for the albino males, 80% for albino females and 80% for male Wistar rats. Thyroid follicular-cell tumours occurred in 8/10 albino male, 8/10 albino female and 6/10 male Wistar rats. The tumour diagnoses included thyroid adenoma, carcinoma and fetal adenoma [authors' terminology]. The incidences of thyroid carcinomas in these groups were 4/10 albino males, 3/10 albino females and 0/10 male Wistar rats. Two of the thyroid carcinomas in the albino rats [sex not specified] metastasized to the lung (Purves & Griesbach, 1947). [The Working Group noted the lack of control groups.]

Groups of 18 albino rats [identified as Osborne-Mendel by Deichmann *et al*. (1967); sex not specified], 21 days of age, were given a diet of ground commercial rat biscuits containing thiourea [purity not specified] at a concentration of 0 (control), 100, 250, 500, 1000, 2500, 5000 or 10 000 mg/kg for 2 years. All rats at concentrations ≥ 2500 mg/kg of diet died before 17 months. Of the 29 treated rats that survived for 2 years, 14 had hepatocellular adenomas [group distribution not stated], with none in 18 controls. Only one treated rat that survived less than 17 months developed a liver tumour [group not stated]. The incidence of spontaneous hepatic tumours in other control groups in the same laboratory was cited as 1%. Thyroid (follicular-cell) hyperplasia was observed, ranging in severity from moderate at 1000 mg/kg of diet to marked at 10 000 mg/kg of diet, but no thyroid tumours were reported (Fitzhugh & Nelson, 1948). [The Working Group noted the small group sizes, the poor survival and the lack of detail provided in this report.]

Groups of 12 and 19 male random-bred albino (Hebrew University strain) rats, weighing approximately 100 g [age not specified], were given drinking-water containing thiourea [purity not specified] at a concentration of 0 (control) or 0.2% for up to 26 months. Epidermoid carcinomas of the external auditory duct or meibomian glands of the eyelids were diagnosed in 17/19 treated rats in contrast to 0/12 control rats.

In a companion study, 16 male rats of the same strain were given intraperitoneal injections of about 3.4–4 mL of a 10% aqueous solution of thiourea three times per week for 6 months, followed by 0.2% thiourea in the drinking-water for up to 22 months. Similar tumours were produced in 10/16 rats (Rosin & Ungar, 1957). A subsequent study from the same laboratory, in which the same strain of rat was given 0.2% thiourea in the drinking-water for 14–23 months, showed squamous-cell carcinomas of the Zymbal gland and/or meibomian gland in 7/8 survivors (Ungar & Rosin, 1960). [The Working Group noted that the rats used in the last study were survivors of tumour transplantation studies in which the intrascapular implant was considered to have failed.]

In a study of the synergistic effects of various carcinogens, groups of 30 male and 30 female Osborne-Mendel rats were fed a diet containing 0 (control) or 80 mg/kg thiourea [purity not stated] from weaning for 104 weeks. Treatment had no effect on the mortality rate, the cumulative rate for the experiment being 65% for males and 60% for females. There was no difference between control and treated groups in tumour incidence at any site examined, including the liver (1/60 in controls and 0/60 in treated rats) (Radomski *et al*., 1965). [The Working Group noted that the concentration of thiourea used, which produced no liver tumours, was only 20% less than the dose that produced a 60% liver tumour incidence in the same rat strain in the study of Fitzhugh and Nelson (1948).]

As part of another study of the synergistic effects of combinations of carcinogens on tumorigenesis, groups of 30 male and 30 female Osborne-Mendel rats were fed 50 mg/kg diet thiourea (purity, 100%) from weaning for 26 months. A control group of 30 males and 30 females fed basal diet was terminated at 25 months. After 24 months, the survival rate of rats receiving thiourea was 51%. There was no increase in tumour incidence at any of the organ sites examined, including the liver, in which there were no tumours observed in either control or treated groups (Deichmann *et al*., 1967).

3.2 Administration with known carcinogens

The studies described below were published since the previous evaluation.

Rat: Thiourea was tested in an initiation–promotion model of liver carcinogenesis in which *N*-nitrosodiethylamine (NDEA) was used as the initiating agent and Clophen A 50 (a technical-grade mixture of polychlorinated biphenyls) as the promoting agent. In the initiating arm, groups of four to six male and female Sprague-Dawley rats, 21–26 days of age, received an oral dose of 200 or 500 mg/kg bw per day thiourea (purity, 99.9%) in 2 mL water by gavage on three consecutive days, followed 6 days later by oral gavage with Clophen A 50 at a dose of 10 mg/kg bw per day in 2 mL olive oil for 11 consecutive weeks. Another four groups received either thiourea, Clophen A 50 or olive oil alone at the same doses. In the promoting arm, two groups of four to six males and females received a single oral gavage dose of 8 mg/kg bw NDEA (purity, 99%), followed 1 week later by thiourea in the drinking-water at a concentration of 0.2% for 51 days. Two additional groups of female rats received 0.05% or 0.1% thiourea in the

drinking-water for 70 days starting 1 week after NDEA treatment. Another two groups of male and female rats received NDEA alone. After 12 weeks, the livers were scored for preneoplastic foci identified by ATPase deficiency. Thiourea did not enhance the incidence of foci of hepatocellular alteration when given either as an initiator or a promoter (Oesterle & Deml, 1988).

Groups of 30 male Fischer 344 rats, 5 weeks of age, received a single subcutaneous injection of 2 g/kg bw *N*-nitrosobis(2-hydroxypropyl)amine (NBHPA), followed 1 week later either by thiourea at a concentration of 0.1% in the drinking-water for 19 weeks or basal diet and water alone. Five animals from each group were killed at various intervals up to the end of the study. From four weeks onwards, thyroid follicular-cell adenomas occurred in 5/20 rats receiving NBHPA plus thiourea, in contrast to 0/20 receiving NBHPA alone (Shimo *et al*., 1994a).

Groups of 10 or 15 male Fischer 344 rats, 5 weeks of age, received a single subcutaneous injection of 1.5 g/kg bw NBHPA, followed 1 week later by thiourea in the drinking-water at a concentration of 0, 0.05 or 0.1% for 20 weeks. A group of 19 control rats received basal diet and distilled water alone. The incidences of thyroid follicular-cell tumours were increased at both doses of thiourea ($p < 0.01$), with 5/10 rats bearing tumours after receiving NBHPA plus 0.05% or 0.1% thiourea, in contrast to 0/15 with NBHPA only and 0/19 untreated controls. All tumours but one (a carcinoma) were thyroid adenomas (Onodera *et al.*, 1994).

Groups of 20 and 15 male Fischer 344 rats, 6 weeks of age, received a single subcutaneous injection of 2 g/kg bw NBHPA, followed 1 week later by thiourea at a concentration of 0 or 0.1% in the drinking-water for 19 weeks. The study was terminated at 20 weeks. Administration of thiourea increased the incidence ($p < 0.01$) of thyroid follicular-cell adenomas, in 10/15 animals given NBHPA plus thiourea and 0/20 given NBHPA only. Thiourea did not promote the induction of hepatocellular tumours to a statistically significant degree (Shimo *et al*., 1994b).

A group of 15 male Fischer 344 rats, 6 weeks of age, received a single subcutaneous injection of 2.8 g/kg bw NBHPA, followed by thiourea at a concentration of 0.2% in the drinking-water for 19 weeks. The study was terminated at 20 weeks. Administration of thiourea increased the incidence of thyroid follicular-cell neoplasms: of the animals given NBHPA plus thiourea, 10/15 had tumours with an adenomatous growth pattern and 6/15 with a solid growth pattern; no tumours were seen in five rats treated with NBHPA alone (Mitsumori *et al*., 1996).

Groups of 10 male Fischer 344 rats, 6 weeks of age, received a single subcutaneous injection of 2.8 g/kg bw NBHPA, followed 1 week later either by thiourea at a concentration of 0.2% in the drinking-water for 10 weeks or basal diet and water alone. Administration of thiourea increased the incidence ($p < 0.01$) of thyroid follicular-cell tumours, which were seen in 10/10 rats given NBHPA plus thiourea and 1/10 given NBHPA only (Takegawa *et al*., 1997).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Thiourea is absorbed from the gastrointestinal tract. A single oral dose of 100 mg of thiourea was almost completely eliminated from the blood within 24 h; 15% was broken down in the intestine and 30–50% in other tissues and body fluids, the remainder (approximately 30%) being excreted as thiourea in the urine (Williams & Kay, 1947).

4.1.2 *Experimental systems*

Thiourea is absorbed from the gastrointestinal tract in rats. In rats given 5 mg by intravenous injection, 30% of the thiourea was recovered from the carcasses after 3 h and only traces after 25 h (Williams & Kay, 1947).

In homogenized liver preparations from female Holtzman rats, 28–35% of added thiourea was metabolized within 3 h. The pathway for the breakdown of thiourea was suggested to be as follows: uracil; β-ureidopropionic acid, which was further metabolized to β-alanine; ammonia and carbon dioxide (Spector & Shideman, 1959).

Thiourea is transferred across the placenta in rabbits and dogs (Shepard, 1963).

Autoradiographic analysis of pregnant NMRI mice given about 0.05 mg of [^{14}C]-thiourea by intravenous injection at a late stage of gestation [gestational age not specified] revealed accumulation of radiolabel in the fetal thyroid (Slanina *et al*., 1973).

[^{14}C]Thiourea administered by intraperitoneal injection bound to liver, kidney and lung protein in male Sprague-Dawley rats (Hollinger *et al*., 1974) and was found to be uniformly distributed in alveolar walls 24 h after dosing (Hollinger *et al*., 1976).

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Male Fischer 344 rats, 4 weeks of age, were given drinking-water containing 0.1 or 0.05% thiourea for 1 week. Dose-dependent decreases were found in the serum concentrations of triiodothyronine [by 60% and 15%, respectively] and thyroxine (T4) [by 85% and 45%, respectively]. A single subcutaneous dose of 1500 mg/kg bw NBHPA given to another group of rats, followed 1 week later by 0.1 or 0.05% thiourea

in the drinking-water for 20 weeks, caused thyroid follicular-cell proliferative lesions and decreased serum T4 concentrations (by < 20%). The concentration of T3 was unchanged, and that of thyroid-stimulating hormone (TSH) was increased by 40% at the higher concentration only (Onodera *et al*., 1994).

Male Fischer 344 rats, 4 weeks of age, were given 0.1% thiourea in the drinking-water for 19 weeks starting 1 week after they had received a single subcutaneous injection of 2000 mg/kg bw NBHPA. Groups of rats were sacrificed at weeks 1, 2, 4, 8, 12 and 16. In comparison with the serum T4 concentration after treatment with NBHPA alone, that in rats given thiourea was decreased by approximately 60% at week 1 and remained significantly reduced throughout the experiment. The serum TSH concentration was elevated; it peaked at 4 weeks (20-fold increase) and returned to normal at 12 weeks. Thyroid weights were significantly increased in a treatment duration-dependent manner. Hyperplasia was noted at 2 weeks and adenomas at 4 weeks, both of which increased with length of treatment. Proliferation was greatest when the TSH concentrations were elevated (Shimo *et al*., 1994a).

Starting 1 week after initial treatment with NBHPA (2800 mg/kg bw) by subcutaneous injection, male Fischer 344 rats were given 0.2% thiourea in the drinking-water for 10 weeks. The treated animals had decreased body weights, increased thyroid weights [fivefold], decreased T4 concentrations [25%] and increased TSH concentrations [fivefold]. Thiourea given with 0.1% vitamin A after initiation with NBHPA resulted in decreased serum concentrations of triiodothyronine and T4 [55% and 75%, respectively] and an increased TSH concentration [13-fold]. Thyroid weight gain was greater with the combined treatment. Thyroid hyperplasias and neoplasias were induced in both groups; however, the combination of thiourea and vitamin A induced more cell proliferation, as measured by bromodeoxyuridine incorporation (Takegawa *et al*., 1997).

Mature (450–500 g) and immature (50–80 g, 21–23 days of age) male Sprague-Dawley rats were given an intraperitoneal dose of 0.6 mg/kg bw of [^{14}C]thiourea. The immature, but not the mature rats were tolerant to the toxic pulmonary effects of this treatment (Hollinger *et al*., 1976). Vascular permeability, as determined by Evans blue dye injected into a femoral vein, increased with the age of male Sprague-Dawley rats that received an intraperitoneal dose of 10 mg/kg bw thiourea 2 h before sacrifice. The increased vascular permeability concorded with increased concentrations of histamine in lung and plasma (Giri *et al*., 1991a).

The lethal intraperitoneal dose of thiourea in male Sprague-Dawley rats was 10 mg/kg bw, causing 100% mortality within 24 h. A non-lethal dose (0.5 mg/kg bw) given as pre-treatment provided complete protection against death for 8 days and partial protection for 24 days. The protection was correlated with histamine concentrations; that is, the histamine concentrations were low when the animals were protected (Giri *et al*., 1991b).

In an assay for iodination with 2-methoxyphenol (guaiacol) in the presence of iodide and thiourea, thyroid peroxidase oxidized thiourea to formamidine disulfide. At

neutral pH, formamidine then decomposed to cyanamide, which inhibited the function of thyroid peroxidase (Davidson *et al*., 1979).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Groups [size unspecified] of CF4 rats were given drinking-water containing 0.2% thiourea on days 1–14 of gestation, and the fetuses were examined on day 20. While the specific incidences of fetal effects were not provided, the authors noted that growth retardation and malformations of the nervous system and skeleton were present in the treated offspring (Kern *et al*., 1980).

4.4 Effects on enzyme induction or inhibition and gene expression

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

After initial treatment of male Fischer 344 rats with NBHPA at 2800 mg/kg bw, administration of 0.2% thiourea in the drinking-water for 10 weeks increased the activities of the cytochrome P450 isozymes CYP2E1 and CYP4A1 in the liver, while the activity of T4-UDP glucuronosyl transferase in the liver was similar to the control value (Takegawa *et al*., 1997).

Thiourea at 10–100 mmol/L (optimum, 25 mmol/L) increased CYP2B1-catalysed oxidation of the tobacco-specific carcinogen 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) in a reconstituted cell-free system (Guo *et al*., 1991).

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)

(*a*) *DNA damage*

Thiourea did not induce differential survival in DNA repair-deficient strains of *Escherichia coli* or forward mutation to induce repair in the SOS chromotest. It produced differential cell killing in *E. coli uvrB/recA* cells without, but not with, metabolic activation. It did not induce mutation in *Salmonella typhimurium umu* and did not induce prophage in *E. coli* K12.

There is disagreement in the literature about the ability of thiourea to induce DNA single-strand breaks. Thiourea decreased the frequency of DNA strand breaks induced by X-rays or intercalating agents in mouse lymphoma cells, probably by altering chromatin structure (Pommier *et al.*, 1983). It did not induce unscheduled DNA synthesis in primary rat hepatocytes.

The reaction of [^{14}C]thiourea and hydrogen peroxide in the presence of calf thymus DNA produced formamidine sulfonate and cyanamide and gave rise to covalent binding of radiolabel to the DNA (Ziegler-Skylakakis *et al.*, 1998). This mechanism has not been observed *in vivo*.

(*b*) *Mutation and allied effects*

Thiourea was not mutagenic to *Salmonella typhimurium* or *E. coli* when tested without or with metabolic activation from liver microsomes from Aroclor-induced rats, mice or hamsters. It was weakly mutagenic in base-pair substitution and frameshift strains of *Salmonella* in the mouse host-mediated assay after intramuscular administration.

Thiourea was mutagenic in *Saccharomyces cerevisiae* and induced intrachromosomal recombination and petite mutations. It did not induce mutation or chromosomal malsegregation in *Aspergillus*.

Thiourea did not induce homologous or non-homologous recombination in cultured Chinese hamster cells.

There is disagreement in the literature about the ability of thiourea to induce mutation in mouse lymphoma L5178Y (*Tk* locus) or Chinese hamster V79 (*Hprt* locus) cells. Mutagenicity in Chinese hamster V79 cells was enhanced by depletion of intracellular glutathione.

Thiourea did not induce sister chromatid exchange in Chinese hamster V79 cells. It induced micronucleus formation in Syrian hamster embryo cells. There was weak induction of micronuclei in Chinese hamster V79 cells.

Thiourea transformed Syrian hamster embryo cells and Rauscher virus-infected rat embryo cells, and had weak transforming ability in a C3H10T1/2 cell line carrying bovine papillomavirus DNA.

Thiourea induced intrachromosomal recombination in transformed human lymphoblastoid cells.

Table 1. Genetic and related effects of thiourea

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli K12, prophage induction	NT	–	2000 µg/plate	Mamber *et al*. (1984)
Escherichia coli, SOS repair, forward mutation	–	–	38 000	Brams *et al*. (1987)
Escherichia coli, SOS repair, forward mutation	–	–	40 µg/tube	Kevekordes *et al*. (1999)
Escherichia coli pol A, differential toxicity (liquid suspension test)	NT	–	250	Rosenkranz & Poirier (1979)
Escherichia coli pol A, differential toxicity (liquid suspension test, other markers)	–	–	5000 µg/well	McCarroll *et al*. (1981)
Escherichia coli uvr/*rec* strains, differential toxicity	+	–	25 000	Hellmér & Bolcsfoldi (1992)
Salmonella typhimurium TA1535/pSK1002, *umu* test	–	–	1670	Nakamura *et al*. (1987)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, TA1536, reverse mutation	–	–	125 µg/plate	Simmon (1979a)
Salmonella typhimurium TA100, reverse mutation	–	–	150 µg/plate	Yamaguchi (1980)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, TA98, reverse mutation	–	–	333 µg/plate	Dunkel *et al*. (1984)
Salmonella typhimurium TA100, TA98, TA97, reverse mutation	–	–	1000 µg/plate	Brams *et al.* (1987)
Salmonella typhimurium TA100, TA1535, TA98, TA97, reverse mutation	–	–	10 000 µg/plate	Zeiger *et al*. (1988)
Salmonella typhimurium TA1535, TA1538, reverse mutation	–	–	250 µg/plate	Rosenkranz & Poirier (1979)
Escherichia coli RK, forward mutation	–	–	10 000	Hayes *et al*. (1984)
Escherichia coli WP2 *uvrA*, reverse mutation	–	–	333 µg/plate	Dunkel *et al*. (1984)
Aspergillus nidulans, mitotic malsegretation or forward mutation	–	NT	10 000	Crebelli *et al*. (1986)
Saccharomyces cerevisiae D3, mitotic recombination	–	–	50 000	Simmon (1979b)
Saccharomyces cerevisiae, intrachromosomal recombination	+	NT	30 000	Schiestl (1989)
Saccharomyces cerevisiae, intrachromosomal recombination	+	NT	20 000	Schiestl *et al*. (1989)
Saccharomyces cerevisiae, intrachromosomal recombination in G_2-arrested cells	+	NT	50 000	Galli & Schiestl (1995)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Saccharomyces cerevisiae, intrachromosomal recombination in G_1-arrested cells	+	NT	10 000	Galli & Schiestl (1996)
Saccharomyces cerevisiae, intrachromosomal recombination in S-phase arrested cells	+	+	10 000	Galli & Schiestl (1998)
Saccharomyces cerevisiae, petite mutation	+	NT	4000	Egilsson *et al*. (1979)
Saccharomyces cerevisiae D3, petite mutation	+	NT	500	Wilkie & Gooneskera (1980)
Saccharomyces cerevisiae, reverse mutation, *trp* locus	–	+	500	Morita *et al*. (1989)
Drosophila melanogaster, somatic recombination, *zest-white* locus	+		7.6 µg/mL feed	Batiste-Alentorn *et al*. (1991)
Drosophila melanogaster, somatic recombination, w/w^+ locus	(+)		38 µg/mL feed	Vogel & Nivard (1993)
Drosophila melanogaster, somatic recombination, *white-ivory* system	?		152 µg/mL feed	Batiste-Alentorn *et al*. (1994)
Drosophila melanogaster, somatic recombination, wing-spot system	?		76 µg/mL feed	Batiste-Alentorn *et al*. (1995)
Drosophila melanogaster, somatic recombination, w/w^+ locus	–		76 µg/mL feed	Rodriguez-Arnaiz (1997)
DNA single-strand breaks, primary rat hepatocytes *in vitro*	+	NT	2280	Sina *et al*. (1983)
DNA single-strand breaks, primary rat hepatocytes *in vitro*	–	NT	1250	Fautz *et al*. (1991)
Unscheduled DNA synthesis, primary rat hepatocytes *in vitro*	–	NT	1900	Lonati-Galligani *et al*. (1983)
Unscheduled DNA synthesis, primary rat hepatocytes *in vitro*	–	NT	10 000	Fautz *et al*. (1991)
Gene mutation, Chinese hamster V79 cells, *Hprt* locus *in vitro*	–	NT	7600	Bradley *et al*. (1982)
Gene mutation, Chinese hamster V79 cells, *Hprt* locus *in vitro*	+	+[c]	760	Ziegler-Skylakakis *et al*. (1985)
Recombination, Chinese hamster V79 cell sub-line Sp5 *in vitro*	–	NT	25	Helleday *et al*. (1998)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	–	5000	Mitchell *et al*. (1988)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	–	(+)	5000	Myhr & Caspary (1988)
Gene mutation, mouse lymphoma L5178Y cells, *Tk* locus *in vitro*	(+)	(+)	1370	Wangenheim & Bolcsfoldi (1988)
Sister chromatid exchange, Chinese hamster V79 cells *in vitro*	–	NT	7600	Bradley *et al*. (1982)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Micronucleus formation, Syrian hamster embryo cells *in vitro*	+	NT	NR	Fritzenschaf *et al*. (1993)
Micronucleus formation, Chinese hamster V79 cells *in vitro*	(+)	NT	760	Ziegler-Skylakakis *et al*. (1998)
Cell transformation, Syrian hamster embryo cells	+	NT	0.1[d]	Pienta *et al.* (1977)
Cell transformation, Rauscher virus-infected rat embryo cells	+	NT	100	Dunkel *et al*. (1981)
Cell transformation, bovine papilloma virus DNA-enhanced C3H10T1/2 cells	(+)	NT	20	Kowalski *et al*. (2000)
Recombination (*HPRT* reversion), transformed human lymphoblastoid GM6804 cells *in vitro*	+	NT	5	Aubrecht *et al*. (1995)
Host-mediated assay, *Salmonella typhimurium* TA1530, TA1538, reverse mutation in mice *in vivo*	(+)		125 im × 1	Simmon *et al.* (1979)

[a] +, positive; –, negative; (+), weak positive; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day; NR, not reported; im, intramuscular

[c] Co-culture with rat hepatocytes

[d] Higher concentrations were inactive.

Thiourea was mutagenic in somatic cells of *Drosophila melanogaster*. It induced mitotic recombination at one locus but not others.

4.6 Mechanistic considerations

Thiourea belongs to a class of drugs used in the treatment of hyperthyroidism and acts by inhibiting thyroid peroxidase, which decreases thyroid hormone production and increases proliferation by increasing the secretion of TSH. This is the probable basis of its thyroid tumour-promoting activity in experimental animals; however, no definitive conclusion regarding the mechanism of carcinogenicity of thiourea can be drawn in view of the mixed results obtained in tests for genotoxicity. Thiourea can interfere with thyroid peroxidase-mediated iodination of thyroglobulin.

Thiourea was not mutagenic in bacteria, but mixed results were obtained in assays in mammalian cells. Thiourea induced chromosomal recombination and mammalian cell transformation. The compound has not been adequately tested for genotoxicity *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Thiourea is used in many industrial applications, including as a chemical intermediate or catalyst, in metal processing and plating and in photoprocessing.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Thiourea has not been tested in a conventional bioassay of carcinogenicity in rodents that would meet present-day standards. In four early studies involving several strains of mice, thyroid hyperplasia but not thyroid tumours was reported after oral administration of thiourea. In several studies in rats given thiourea orally, either a high incidence of thyroid follicular-cell adenomas and carcinomas or increased incidences of hepatocellular adenomas or tumours of the Zymbal or meibomian glands were reported. However, there were deficiencies in each of these studies and no correspondence between studies with respect to tumour site. In five initiation–promotion studies in rats, thiourea promoted thyroid follicular-cell tumours initiated by *N*-nitrosobis(2-hydroxypropyl)amine.

5.4 Other relevant data

Thiourea is well absorbed and concentrates in the thyroid. It is readily excreted. It can cross the placental barrier. Thiourea acts by inhibiting thyroid peroxidase, resulting in decreased thyroid hormone production and increased proliferation due to an increase in the secretion of thyroid-stimulating hormone. This is the probable basis of the tumorigenic activity of thiourea for the thyroid in experimental animals.

No data were available on reproductive or developmental effects of thiourea in humans. One study in rats showed growth retardation and malformations of the skeleton and nervous system in the offspring of thiourea-treated animals.

Thiourea did not induce gene mutation in bacteria, but mixed results were obtained in assays in mammalian cells. It consistently induced chromosomal recombination in yeast and insects and induced mammalian cell transformation.

5.5 Evaluation

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

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

Overall evaluation

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

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