PROPYLTHIOURACIL

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.

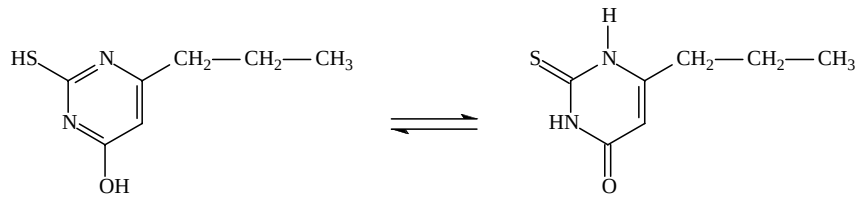
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 51-52-5
Deleted CAS Reg. No.: 500-50-5
Chem. Abstr. Name: 2,3-Dihydro-6-propyl-2-thioxo-4(1*H*)-pyrimidinone
IUPAC Systematic Name: 6-Propyl-2-thiouracil
Synonyms: 6-*n*-Propyl-2-thiouracil; 6-*n*-propylthiouracil; 6-propyl-2-thio-2,4-(1*H*,3*H*)pyrimidinedione; 6-propylthiouracil; PTU; 2-thio-4-oxy-6-propyl-1,3-pyrimidine; 2-thio-6-propyl-1,3-pyrimidin-4-one

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_7H_{10}N_2OS$ Relative molecular mass: 170.24

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White to pale-cream crystals or microcrystalline powder (Aboul-Enein, 1977; Lide & Milne, 1996; Budavari, 2000)
(*b*) *Melting-point*: 219 °C (Lide & Milne, 1996)
(*c*) *Spectroscopy data*: Infrared [prism (25719), grating (1591)], ultraviolet (9305), nuclear magnetic resonance [proton (8367)] and mass spectral data have been reported (Sadtler Research Laboratories, 1980; Lide & Milne, 1996).
(*d*) *Solubility*: Slightly soluble in water, chloroform and ethanol; insoluble in benzene and diethyl ether (Lide & Milne, 1996)

1.1.4 *Technical products and impurities*

Propylthiouracil is available as 25- or 50-mg tablets (Gennaro, 1995; American Hospital Formulary Service, 2000; Herbrand, 2000).

Trade names for propylthiouracil include Procasil, Propacil, Propycil, Propyl-Thiocil, Propyl-Thyracil, Propylthiorit, Prothiucil, Prothiurone, Prothycil, Prothyran, Protiural, Thiuragyl, Thyreostat II and Thiotil.

1.1.5 *Analysis*

Several international pharmacopoeias specify infrared absorption spectrophotometry with comparison to standards, thin-layer chromatography and colorimetry as methods for identifying propylthiouracil; potentiometric titration and titration with sodium hydroxide are used to assay its purity. In pharmaceutical preparations, propylthiouracil is identified by infrared and ultraviolet absorption spectrophotometry and high-performance liquid chromatography (HPLC) with ultraviolet detection; HPLC with ultraviolet detection and titration with sodium hydroxide or mercury nitrate are used to assay for propylthiouracil content (British Pharmacopoeial Commission, 1993; Society of Japanese Pharmacopoeia, 1996; Council of Europe, 1997; AOAC International, 1998; US Pharmacopeial Convention, 1999).

Methods have been reported for the analysis of propylthiouracil in biological fluids (blood, milk, serum, urine), tissues, dried animal feed, feed additives and drugs. The methods include potentiometric titration, capillary zone electrophoresis with ultraviolet detection, micellar electrokinetic chromatography, thin-layer chromatography, high-performance thin-layer chromatography, HPLC with atmospheric pressure chemical ionization mass spectrometry, reversed-phase HPLC with ultraviolet detection and gas chromatography with mass spectrometry (Saldaña Monllor *et al*., 1980; Moretti *et al.*, 1986, 1988; Centrich Escarpenter & Rubio Hernández, 1990; De Brabander *et al*., 1992; Moretti *et al.*, 1993; Kriványková *et al*., 1996; Blanchflower *et al*., 1997; Ciesielski & Zakrzewski, 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

Propylthiouracil can be prepared by the condensation of ethyl β-oxocaproate with thiourea (Anderson *et al.*, 1945).

Information available in 2000 indicated that propylthiouracil was manufactured by three companies in Germany, two companies in Japan and one company in Brazil (CIS Information Services, 2000a).

Information available in 2000 indicated that propylthiouracil was used in the formulation of pharmaceutical drugs by four companies in the USA, three companies in Germany, two companies each in Austria, Canada, Thailand and the United Kingdom and one company each in Australia, Belgium, Brazil, Israel, Japan, Portugal, the Republic of Korea, Singapore, Sweden, Switzerland and Turkey (CIS Information Services, 2000b).

1.3 Use

Propylthiouracil has been used since the 1940s in the treatment of hyperthyroidism. The starting doses are usually 100–150 mg three times a day orally; higher doses, up to 2400 mg/day, have been used in severe thyrotoxicosis. There are no intravenous preparations, but rectal use has been reported (Cooper, 1998). The dose of propylthiouracil is not different for infants, children or the elderly, and it is considered unnecessary to alter the dose for patients with hepatic or renal disease (Cooper, 2000). In the USA, propylthiouracil is used as the primary therapy for hyperthyroidism in pregnancy (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. Propylthiouracil has also been deemed safe for use by lactating women (Cooper, 1987; Momotani *et al.*, 2000).

Anti-thyroid drugs, including propylthiouracil, may be given for several weeks up to 1–2 years for the treatment of hyperthyroidism. 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 doses of anti-thyroid drug can be reduced. For example, maintenance doses of 50–150 mg of propylthiouracil per 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).

Propylthiouracil has been investigated as a possible therapy for alcoholic hepatitis (Orrego *et al.*, 1987), the rationale being that the induction of a hypothyroid state might decrease hepatic oxygen requirements, or that propylthiouracil might function

as a free-radical scavenger. However, this use has not gained much support (Orrego *et al*., 1994).

By inducing hypothyroidism, propylthiouracil can increase the body weight of cattle (Thrift *et al*., 1999), but the use of thyrostatic drugs for this purpose is forbidden in the European Union (European Commission, 1981) and by the Department of Agriculture (2000) in the USA.

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 3300 workers, comprising mainly pharmacists and laboratory workers in health services, were potentially exposed to propylthiouracil in the USA.

1.4.2 *Environmental occurrence*

No data were available to the Working Group.

1.5 Regulations and guidelines

Propylthiouracil is listed in the pharmacopoeias of China, France, Germany, Japan, the United Kingdom and the USA and also in the European and International Pharmacopoeias (Society of Japanese Pharmacopoeia, 1996; Council of Europe, 1997; Royal Pharmaceutical Society of Great Britain, 2000; Swiss Pharmaceutical Society, 2000), and it is registered for human use in Norway, Sweden, Portugal and the United Kingdom (Instituto Nacional de Farmacia e do Medicamento, 2000; Medical Products Agency, 2000; Medicines Control Agency, 2000; Medicines Evaluation Board Agency, 2000; Norwegian Medicinal Depot, 2000).

2. Studies of Cancer in Humans

No information was available specifically on propylthiouracil.

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 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

Propylthiouracil was evaluated in a previous monograph (IARC, 1974). Because there have been only four new studies on the carcinogenicity of propylthiouracil in animals and none that are conventional bioassays in rodents, the most relevant studies from the previous monograph were analysed in greater depth. Studies on the carcinogenicity of anti-thyroid chemicals, including propylthiouracil, in experimental animals have been reviewed (Doniach, 1970; Christov & Raichev, 1972; Paynter *et al*., 1988).

3.1 Oral administration

Mouse: Groups of male strain A mice [initial numbers not specified, but presumed to be four], 4–6 weeks of age, received a commercial diet containing 0.8% propylthiouracil [purity not specified] for up to 534 days. Thyroid follicular-cell carcinomas (two of which metastasized to the lungs) were present in all four propylthiouracil-treated mice and chromophobe adenomas of the anterior lobe of the pituitary gland in three of these mice. The anterior pituitary glands of a similar group of surgically thyroidectomized mice were normal (Moore *et al*., 1953). [The Working Group noted the small numbers of animals in the groups.]

Groups of 60 C57BL mice [sex not specified], 4–5 weeks of age, were fed a diet containing propylthiouracil [purity not specified] at a concentration of 0 (control), 10 or 12 g/kg of diet for 17 months. The survival rate in all groups was approximately 50%. Pituitary adenomas occurred in 15/24 and 21/29 mice at the two concentrations, respectively, and in 0/28 control mice. Thyroid follicular-cell hyperplasia was grossly apparent in the treated mice. Administration of 2,4-dinitrophenol (an inhibitor of thyrotropin release) at 0.5 g/kg of diet in conjunction with the two doses of propylthiouracil reduced the incidence of pituitary tumours by at least 75% in each case, and no thyroid hyperplasia was apparent in these mice (King *et al*., 1963).

Rat: Two groups of young adult white rats [number per group, sex, age and strain not specified] were given drinking-water containing propylthiouracil [purity not specified] at a concentration of 0.1%. One of the groups received propylthiouracil and potassium iodide alternately, the latter at a concentration of 0.01% in the drinking-water [exact protocol not stated]. The study was terminated within 1 year, when the

total survival rate in the two groups was 44 of the original 100 rats. Thyroid follicular-cell tumours occurred in 4/15 survivors given propylthiouracil alone and in 20/29 survivors treated with propylthiouracil and potassium iodide alternately. All but one of the tumours were thyroid adenomas, the exception being a thyroid carcinoma in a rat given propylthiouracil plus potassium iodide (Zimmerman *et al*., 1954).

Groups of male and female Wistar rats [group size presumed to be 55 of each sex], 6–8 weeks of age, received propylthiouracil [purity not specified] at a concentration of 0.2% in their drinking-water alone or after a single intraperitoneal injection of 30 μCi of ^{131}I. Because of a high mortality rate, the concentration of propylthiouracil given to both groups was reduced to 0.1% at 3 months, 0.05% at 6 months and 0.025 % at 1 year. In a second part of the experiment, 25 rats [number of each sex not specified] received a low concentration of propylthiouracil in their drinking-water, adjusted to provide a dose of 7 mg/kg bw per day initially (approximately equivalent to the human clinical dose) and then reduced to 1 mg/kg bw per day over 3 months. The control groups comprised 20 untreated male and 20 untreated female rats on normal diet. The treatments were continued until termination at 18 months, but control rats were continued until approximately 20 months of age. In the groups receiving 0.2% propylthiouracil alone, thyroid follicular-cell adenomas occurred in 11/18 males and 20/30 females and thyroid carcinomas in 3/18 males and 4/30 females. In the groups receiving 0.2% propylthiouracil plus ^{131}I, thyroid adenomas occurred in 9/15 males and 16/24 females and thyroid carcinomas in 4/15 males and 6/24 females. In the groups that initially received propylthiouracil at 7 mg/kg bw per day, thyroid adenomas occurred in 2/5 males and 7/13 females and thyroid carcinomas in 1/5 males and 2/13 females. In the untreated control groups, thyroid adenomas occurred in 2/20 males and 1/20 females, but there were no carcinomas in either sex (Willis, 1961).

Groups of 99–112 male Long Evans rats, 6 weeks of age, were fed a diet containing propylthiouracil [purity not specified] at a concentration of 0.1% (100 rats), the same diet after a single intraperitoneal injection of 25 μCi of ^{131}I in 0.5 mL of distilled water (112 rats), propylthiouracil in combination with ^{131}I plus dessicated thyroid powder at a concentration of 250 mg/kg of diet (99 rats) or propylthiouracil plus dessicated thyroid powder (99 rats). Additional groups consisted of untreated controls (101 rats), rats receiving ^{131}I only (106 rats), rats receiving dessicated thyroid powder only (103 rats) and rats receiving ^{131}I plus dessicated thyroid powder (106 rats). Each group was maintained on its specific diet for 1 year, at which time the study was terminated. In the group receiving 0.1% propylthiouracil alone, thyroid follicular-cell adenomas occurred in 16/33 survivors. With propylthiouracil in combination with ^{131}I, 23/35 rats had thyroid adenomas, while in the group given propylthiouracil plus ^{131}I plus dessicated thyroid powder, 64/65 rats developed thyroid tumours, of which 51 were adenomas and 13 carcinomas. In the group given propylthiouracil plus dessicated thyroid powder, 43/60 rats developed thyroid tumours, of which 39 were adenomas and 4 carcinomas. None of 68 untreated control rats had adenomas or papillary or follicular carcinomas (Lindsay *et al*., 1966).

In a study published since the previous evaluation, groups of four to six male albino rats, 4 months of age, were given propylthiouracil [purity not specified] in the drinking-water at a concentration of 60 μg/mL for 3, 5, 7 or 9 months 1 week after a single intraperitoneal injection of 25 μCi of ^{131}I in 0.5 mL of saline with or without L-thyroxine in the drinking-water at a concentration of 0.5 μg/mL. Control groups of four rats received no irradiation, propylthiouracil or thyroxine. In the groups given ^{131}I plus propylthiouracil, thyroid tumours occurred in 1/4, 5/5 and 6/6 rats at 5, 7 and 9 months, respectively. In the groups given ^{131}I plus propylthiouracil plus thyroxine, thyroid follicular-cell tumours occurred in 1/4 and 5/5 rats at 7 and 9 months, respectively. There were no thyroid tumours in the control rats (Al-Hindawi *et al*., 1977). [The Working Group noted the small numbers of animals in each group.]

Hamster: Groups of 214 male and 197 female Syrian golden hamsters, 3 months of age, were given drinking-water containing propylthiouracil [purity not specified] at a concentration of 0.2% for up to 133 weeks for males and 113 weeks for females. A control group of 205 males and 146 females were fed a diet with no propylthiouracil. The survival rate was reported not to be markedly influenced by treatment, the mean lifespans being 636, 500, 568 and 500 days for control males and females and treated males and females, respectively. Twelve animals per group were selected for eight interim killings for biochemical analyses. Thyroid follicular-cell cancer was diagnosed in 13/58 males and 9/44 females exposed to propylthiouracil, and an additional four males and six females had thyroid cancer that had metastasized to the lungs or lymph nodes. The thyroid tumour incidence in the control hamsters was not given, but a historical control incidence of 1.5% was cited (Fortner *et al*., 1960). The combined tumour incidence for males and females treated with propylthiouracil was statistically significantly greater than 1.5% ($p < 0.01$) (Sichuk *et al*., 1968). [The Working Group noted the lack of data on concurrent controls.]

Guinea-pig: Groups of 20 male guinea-pigs weighing 600–900 g [age and strain not specified] were given propylthiouracil [purity not specified] in their drinking-water at a concentration of 0.03% for up to 24 months, with or without a series of seven subcutaneous injections of 1 mL of thyroid-lipid extract emulsified in physiological saline given over the course of the study. Two groups of five control animals received the same regimen but without propylthiouracil. The survival rate at the end of the study at 24 months was 30–35% in the propylthiouracil-treated groups and 60% in the control groups. The incidence of animals with thyroid follicular-cell adenomas was 3/20 with propylthiouracil only and 12/20 with propylthiouracil plus thyroid-lipid extract, in contrast to none in either control group (Hellwig & Welch, 1963).

3.2 Administration with known carcinogens

Four studies in which rats were treated with propylthiouracil in combination with known carcinogens have been published since the previous evaluation.

Groups of female Fischer 344 rats, 50 days of age, received a single intravenous injection of *N*-methyl-*N*-nitrosourea (MNU) at a dose of 50 mg/kg bw. Five days later, groups of 30 rats were given propylthiouracil [purity not specified] in their drinking-water at concentrations of 0.3, 1.0 or 3.0%. A control group of 12 rats received no treatment, and 43 rats received the initiating dose of MNU alone. The incidence of thyroid follicular-cell tumours was increased from 0/12 controls and 0/43 receiving MNU only to 12/30, 30/30 and 30/30 with the increasing doses of propylthiouracil, respectively (Milmore *et al*., 1982).

Two groups of 21 male inbred Wistar rats, 6 weeks of age, were fed basal diet containing propylthiouracil [purity not specified] at a concentration of 0.15% either alone or in combination with a single intraperitoneal injection of *N*-nitrosobis(2-hydroxypropyl)amine (NBHPA) at the start of the study at a dose of 2.8 g/kg bw. Two additional groups received the initiating dose of NBHPA alone or basal diet alone (control group). The animals were maintained for 20 weeks, at which time the survival rate was 100%. Thyroid follicular-cell tumours occurred in 21/21 rats given NBHPA plus propylthiouracil, 4/21 given NBHPA only ($p < 0.05$) and 0/21 given propylthiouracil only or no treatment. Of the rats given NBHPA plus propylthiouracil, seven of those bearing thyroid tumours had thyroid carcinomas (Kitahori *et al*., 1984).

Two groups of 20 male inbred Wistar rats, 8 weeks of age, were given basal diet containing propylthiouracil [purity not specified] at a concentration of 0.1% for 19 weeks either alone or in combination with a single intraperitoneal injection of NBHPA (purity, 99.8%) at 7 weeks of age at a dose of 2.8 g/kg bw. Two additional groups received the initiating dose of NBHPA alone or basal diet alone. The survival rate at the end of the experiment was 100% for all groups. Thyroid follicular-cell adenomas occurred in 19/20 rats receiving NBHPA plus propylthiouracil, 1/20 treated with NBHPA alone ($p < 0.05$) and 0/20 receiving propylthiouracil or basal diet alone (Hiasa *et al*., 1987).

Female Sprague-Dawley rats, 50–60 days of age, were given 7,12-dimethylbenz[*a*]anthracene (DMBA) in sesame oil by oral gavage at a dose of 6.5, 10, 13.5 or 15 mg per animal. Propylthiouracil was given in the drinking-water at concentrations between 0.5 and 4.0 mg/100 mL for various times before and after the DMBA treatment, ranging from 17 days before DMBA up to the end of the study at 4 months. Severe hypothyroidism produced by administration of propylthiouracil at the higher dose from 7 days before DMBA up to study termination reduced the mammary tumour incidence from 68/108 in rats given DMBA only to 3/45 in those given DMBA plus propylthiouracil (Goodman *et al*., 1980).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

In seven healthy persons (six men and one woman) given an intravenous injection of 400 mg of propylthiouracil, the average half-time of the drug was 77 min. In a two-compartmental equation, the total clearance was calculated to be 112 mL/min per m^2. When the same dose was given orally, the average maximum serum concentration of propylthiouracil was 9.1 μg/mL and was reached at 57 min (average for the seven subjects). The total volume of distribution was calculated to be 30% of the body weight, and the bioavailability of propylthiouracil was determined to be 77% (range, 53–88%) (Kampmann & Skovsted, 1974). After intravenous infusion of propylthiouracil into three men and one woman, the half-time and total body clearance were similar to those after injection, but the total volume of distribution (40%) was slightly larger (Kampmann, 1977). In another study, oral administration of a smaller dose of propylthiouracil (200 mg) to six subjects showed a similar half-time, *viz* 1.1 h (Sitar & Hunninghake, 1975). Ringhand *et al*. (1980) calculated a half-time of 1.24–1.4 h after oral administration of propylthiouracil.

In a study in which propylthiouracil was given as a single oral dose of 300 mg to eight healthy volunteers (five women and three men) in either the fasting state or after a standardized breakfast, absorption of the drug was found to be influenced by inter-individual variation but to only a minor extent by food intake (Melander *et al*., 1977). The severity of hyperthroidism and prior exposure to propylthiouracil were reported to affect the rate of elimination after oral administration of 3 mg/kg bw to 10 women and seven men. In patients with mild to moderate hyperthyroidism, elimination of the first dose of propylthiouracil was faster than the elimination in the same individual after 1 month of therapy, whereas in patients with severe hyperthyroidism, elimination of the first dose was inhibited. No changes in absorption rate were reported (Sitar *et al*., 1979).

When patients undergoing thyroidectomy were given [^{35}S]propylthiouracil orally at 100 μCi 3–48 h before surgery, the compound accumulated in the thyroid but not in thyroid neoplasms (Marchant *et al*., 1972).

In one person given 51 mg of [^{35}S]propylthiouracil orally, propylthiouracil glucuronide was the major excretion product (86%) in urine between 0 and 6 h, whereas at 8.8–23 h, a sulfate conjugate was the major urinary metabolite (Taurog & Dorris, 1988).

Placental transfer of [^{35}S]propylthiouracil was examined in four women who were 8–16 weeks pregnant and undergoing therapeutic abortions. The women were given 15 mg (100 μCi) of propylthiouracil orally. The average fetal:maternal serum ratio of radiolabel, obtained for two women, was 0.31. Accumulation of radiolabel in the fetal

thyroid was noted (Marchant *et al*., 1977). Six pregnant hyperthyroid women were given an oral dose of 100 mg of propylthiouracil. The serum profiles of the drug during the third trimester of pregnancy were qualitatively similar to those in non-pregnant women, but the concentrations were consistently lower in the late third trimester than those seen *post partum*. The cord serum concentrations were higher than those in maternal serum collected simultaneously (Gardner *et al*., 1986).

In isolated, perfused, term human placentae, propylthiouracil at doses of 4 and 40 μg/mL in either a protein-free perfusate or a perfusate containing 40 g/L bovine serum albumin readily crossed the placenta and reached equilibrium within 2 h. The binding of propylthiouracil to bovine serum albumin, measured by ultrafiltration, was 94.5% and that to human serum albumin was 60.6%. The transfer of propylthiouracil was similar to that of methimazole (Mortimer *et al*., 1997).

4.1.2 *Experimental systems*

In male Sprague-Dawley rats given [^{14}C]propylthiouracil intravenously, intraperitoneally or orally at a dose of 20 mg/kg bw, equilibrium dialysis indicated that 57% of the drug in plasma was bound to protein. No particular affinity for any tissue was noted. Between 75% and 90% of the administered radiolabel was excreted in the urine and approximately 15% in the bile. The half-time was 4–6 h by all routes of administration. Between 9 and 15% of the initial dose was excreted unchanged within 24 h. The major urinary metabolite was propylthiouracil glucuronide (40–48% in 24-h urine samples), but a different glucuronide conjugate of propylthiouracil appeared to be excreted in bile (Sitar & Thornhill, 1972). Another group of rats given [^{35}S]propylthiouracil intraperitoneally at 1.2 μmol [204 μg] per animal showed accumulation of the propylthiouracil in the thyroid (Marchant *et al*., 1972). Other authors have reported a similar bile metabolite (Papapetrou *et al*., 1972; Lindsay *et al*., 1974; Taurog & Dorris, 1988). Taurog and Dorris (1988) reported that propylthiouracil was the main excretion product, accounting for 34% of the administered radiolabel, and propylthiouracil glucuronide accounted for 32%. In a study with both [^{14}C]- and [^{35}S]propylthiouracil in the same strain of rats, unaltered propylthiouracil comprised 42% of the total urinary output, an unidentified metabolite 22% and propylthiouracil glucuronide 16%. Additional minor metabolites have been reported in both urine and bile (Lindsay *et al*., 1974).

In CD rats given drinking-water containing propylthiouracil at concentrations of 0.0001–0.01% for 1 week or 1 month, the compound was cleared from the serum by bi-exponential disappearance, and an initial increase in the thyroid content of propylthiouracil was seen. Thereafter, the concentration in the thyroid declined linearly (Cooper *et al*., 1983).

In the same strain of rats and with a radioimmunoassay specific for propylthiouracil, the serum concentration was reported to be a linear function of the dose (0.0001–0.05% in drinking-water), while the thyroid concentration was a linear function of the logarithm of the dose. The serum propylthiouracil concentrations were higher after

1 month of treatment than after 1 week. These results were consistent with a multi-compartmental model for the distribution of propylthiouracil (Halpern *et al*., 1983).

Placental transfer of ^{14}C-labelled propylthiouracil was demonstrated in pregnant rats on day 14 of gestation after injection of 1 μCi of the compound. The label was cleared from the fetus within 24 h (Hayashi *et al*., 1970).

When Sprague-Dawley rats were given intravenous injections of [^{14}C]propylthiouracil (4.1 μmol [698 μg]) on days 19 and 20 of gestation, the fetal:maternal serum concentration ratio was < 1 during 2 h after injection (Marchant *et al*., 1977).

Nakashima *et al*. (1978) reported that the intrathyroidal metabolism of propylthiouracil in male Sprague-Dawley rats was strongly influenced by the dose (0.18–59 μmol [31 μg–10 mg] intraperitoneally). Propylthiouracil inhibited its own intrathyroidal metabolism.

Metabolism of propylthiouracil in activated neutrophils resulted in three oxidized metabolites: propylthiouracil-disulfide, propyluracil-2-sulfinate and propyluracil-2-sulfonate. The metabolism was inhibited by sodium azide and catalase and by propylthiouracil itself (Waldhauser & Uetrecht, 1991).

The metabolism of the drug was either reversible or irreversible, depending on iodination conditions, in an in-vitro system containing thyroid peroxidase. Propylthiouracil disulfide was the earliest detectable metabolite (Taurog *et al*., 1989).

4.1.3 *Comparison of animals and humans*

In both humans and laboratory animals, propylthiouracil is quickly absorbed and uniformly distributed, apart from concentration in the thyroid of adults and fetuses. It is rapidly excreted, the main metabolite being a glucuronide in both humans and rats.

4.2 Toxic effects

4.2.1 *Humans*

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

Propylthiouracil 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. In addition, and unlike methimazole, propylthiouracil inhibits type-1 deiodinase which converts T4 to T3 in the liver and other tissues (Cooper, 2000). Therefore, serum T3 concentrations fall rapidly after administration of propylthiouracil, sooner than would be expected on the basis of inhibition of thyroidal hormone synthesis.

In some studies, hyperthyroid patients became hypothyroid if the dose of propylthiouracil was not monitored carefully. In one study, 56% of patients became hypothyroid within 12 weeks while taking 400 mg/day (Kallner *et al*., 1996). With respect to

its effects on T4 deiodination, both normal and hyperthyroid patients showed marked decreases in serum T3 concentrations within a few hours of ingesting 50–300 mg of propylthiouracil. The concentration of T3 decreased by up to 50% in hyperthyroid patients, and that of reverse T3 (rT3), an inactive metabolite of T4 that is cleared by type-1 deiodinase (see Figure 1, General Remarks), increased by up to 50% (Cooper *et al.*, 1982). Ten patients with primary hypothyroidism (eight women and two men), who had been receiving 0.1 or 0.2 mg of T4 daily for ≥ 2 months, were given 1000 mg of propylthiouracil daily in combination with 0.1 mg of T4 for 7 days. The average serum T3 concentration decreased from approximately 80 to 60 ng/100 mL, the average concentration of thyroid-stimulating hormone (TSH) increased gradually from approximately 30 to 40 μU/mL (not statistically significant for the whole group), and no changes occurred in T4 concentrations (Saberi *et al.*, 1975). Similar changes were seen when six healthy volunteers (three men and three women) who had been treated with T4 at 200–250 μg/day for 9 days were given 150 mg of propylthiouracil orally four times a day for 5 days. Thus, the T3 serum concentration was reduced and that of rT3 was enhanced. The concentrations rapidly returned to normal after cessation of treatment with propylthiouracil (Westgren *et al.*, 1977). Similar effects were noted when a dose of 200 mg of propylthiouracil was given orally four times a day for 5 days to 19 hypothyroid patients (six men and 13 women) who had been taking 50–200 μg of T4 per day for ≥ 2 months before the study; however, no changes in TSH concentration were seen (Siersbaek-Nielsen *et al.*, 1978).

(*b*) *Other studies in humans*

Most of the toxic effects of propylthiouracil are considered to be allergenic, including fever, skin rashes and arthralgia, which occur in 1–10% of patients. Agranulocytosis is the most significant major side-effect, occurring in 0.1–0.5% of patients. (Van der Klauw *et al.*, 1998; Cooper, 1999). Other rare but serious reactions include toxic hepatitis (Williams *et al.*, 1997), vasculitis (often antineutrophil cytoplasmic antibody-positive) (Gunton *et al.*, 1999) and a drug-induced lupus syndrome.

4.2.2 *Experimental systems*

In female NMRI mice fed a low-iodine diet, administration of drinking-water containing 0.1% propylthiouracil impaired thyroidal uptake of ^{125}I (Ahrén & Rerup, 1987).

The inhibition of thyroid iodide peroxidase (TPO) by propylthiouracil was studied *in vivo* and *in vitro* by measuring oxidized iodide. Propylthiouracil was given at a dose of 10 mg by intraperitoneal injection to Wistar rats weighing about 150 g. The activity of TPO in the thyroid gland isolated after 3 h was significantly decreased before dialysis and restored after dialysis. *In vitro*, the activity of TPO was decreased by incubation with propylthiouracil and restored by dialysis and by dilution. Propylthiouracil interacted directly with the product of TPO (the oxidized iodide) without significantly

affecting the activity of TPO itself. At a concentration of 2×10^{-6} mol/L, 50% inhibition occurred (Nagasaka & Hidaka, 1976). In male CD rats given propylthiouracil by intraperitoneal injection at 10–50 mg/kg bw in the absence of oxidizable substrates, irreversible inhibition of TPO was observed. When iodide or thiocyanate was present, inhibition was prevented, suggesting that the initial action of propylthiouracil is to block iodination by trapping oxidized iodide (Davidson *et al*., 1978). In an iodination system, inactivation of TPO by propylthiouracil involved a reaction between propylthiouracil and the oxidized haem group produced by interaction between TPO and H_2O_2 (Engler *et al.*, 1982a). A specific inhibitory effect of propylthiouracil on coupling was demonstrated in an incubation system in which TPO catalysed conversion of diiodotyrosine to T4 (Engler *et al*., 1982b).

When male Sprague-Dawley rats maintained on T4 at 20 or 50 μg/kg bw per day were given propylthiouracil, the conversion of T4 to T3 was inhibited (Oppenheimer *et al*., 1972). Frumess and Larsen (1975) further studied the role of the conversion of T4 to T3 in thyroidectomized, hypothyroid male Sprague-Dawley rats that were given a subcutaneous injection of T4 at 8 or 16 μg/kg bw per day, with or without an intraperitoneal injection of propylthiouracil at 10 mg/kg bw per day. The rats were killed after 5, 10, 12 or 15 days. At 5 days, propylthiouracil treatment had increased the serum T4 concentration (from 4.9 to 5.7 μg/100 mL) and decreased that of T3 (from 37 to 19 ng/100 mL), resulting in a marked increase in the serum T4:T3 ratio (from 134 to 329). The serum TSH concentration was increased from 165 to 339 μU/mL in propylthiouracil-treated groups, and their weight gain was slower. When daily doses of 30 mg/kg bw were administered orally for 5 weeks to male Sprague-Dawley rats, both the T3 and T4 concentrations in serum were decreased, and a decrease in iodine incorporation was also noted. Increases in TSH concentration, thyroid weight and hyperplasia of the follicular cells were also reported (Takayama *et al*., 1986). When propylthiouracil was administered to rats in the diet at 30 mg/kg from 3 up to 90 days, it reduced the T3 concentration by 60% and that of T4 by 90%, and increased the thyroid weight (fivefold) and the TSH concentration by more than eightfold. Thyroid-cell proliferation increased by up to 8.5-fold during the first week but had returned to control levels by 45 days (Hood *et al*., 1999a). Hood e*t al*. (1999b) also correlated TSH concentrations with thyroid weight and with the rate of thyroid follicular-cell proliferation in male Sprague-Dawley rats treated with propylthiouracil (1–300 mg/kg of diet) for 21 days. They suggested that small increases in TSH concentration are sufficient to stimulate thyroid follicular-cell proliferation.

Male Wistar rats were given drinking-water containing 0.01% propylthiouracil for 6 months. The drug first acted on the peripheral metabolism of T4 and subsequently on that of TSH. This induced a rapid increase in plasma TSH concentration during the first week, similar to increases seen in other strains of rats. The TSH plasma concentration had returned to normal by day 17, but then increased continuously until the end of treatment. The pituitary TSH concentration decreased after 24 h of treatment and remained low for 3 weeks, then recovered to normal after 1 month. The thyroid weight

increased regularly throughout treatment, and the intrathyroid iodine concentration had decreased by 30-fold after 1 month. Secretion of TSH from the pituitary was found to decrease during the first week of treatment, to recover between 17 days and 1 month, and then to increase again by fourfold with continued treatment. The half-time of TSH was shown to be prolonged by propylthiouracil treatment (Griessen & Lemarchand-Béraud, 1973).

In other studies in male Wistar rats on the secretion of thyroid hormones, infusion of propylthiouracil for 4 h at a rate of 2 mg/h increased the excretion of rT3 in the bile of rats that had also received an infusion of T4, starting 2 h before the propylthiouracil treatment. Infusion of propylthiouracil at 0.05–0.4 mg over 2 h after a pulse of 1 μg of rT3 by intravenous injection increased excretion of rT3 in bile in a dose-dependent manner (Langer & Gschwendtová, 1992). Propylthiouracil at 0.05% in the diet also stimulated excretion of T4 in the bile and faeces of Wistar rats. The compound also stimulated uptake of T4 in liver tissue *in vitro* (Yamada *et al.*, 1976).

In male Wistar rats given propylthiouracil at a concentration of 0.1% in drinking-water for 20 days (calculated intake, 16 mg/day) and an intraperitoneal injection of 100 μCi of ^{125}I 24 h before sacrifice, the amount of soluble thyroglobulin was decreased by > 50% and the proportion of particulate thyroglobulin was slightly increased. The thyroglobulin from treated animals was poorly iodinated. Incubation of thyroid tissue with propylthiouracil *in vitro* inhibited thyroglobulin biosynthesis (Monaco *et al.*, 1980).

In liver homogenates from male Wistar rats, the conversion of T4 to T3 was lower in those from rats given 0.05% propylthiouracil in a low-iodine diet. A graded dose of T4 failed to restore conversion activity in these rats (Aizawa & Yamada, 1981). In monolayers of freshly isolated rat hepatocytes, outer-ring deiodination of an intermediate in thyroid hormone metabolism (3,3′-diiodothyronine sulfate) was completely inhibited by 10^{-4} mol/L propylthiouracil, essentially with no effect on overall 3,3′-diiodothyronine clearance (Otten *et al.*, 1984).

Using a sensitive, specific radioimmunoassay for propylthiouracil, Cooper *et al.* (1983) examined the effects of propylthiouracil at 0.0001–0.01% in drinking-water for 1 week or 1 month in CD rats. A strong inverse relationship was found between the dose of propylthiouracil and both thyroid hormone biosynthesis and peripheral T4 deiodination. The time for recovery from long-term (1 month) treatment was greater than that from short-term (1 week) treatment (2.8 *vs* 1.1 days), although the two treatments had quantitatively similar effects on thyroid function.

Whereas 30 mg/kg bw propylthiouracil given to rats daily for 5 weeks increased thyroid weight sevenfold and decreased both T3 and T4 concentrations by 70%, the same treatment produced no changes in the thyroid in squirrel monkeys (*Saimiri sciureus*). The concentration of propylthiouracil required to inhibit thyroid peroxidase *in vitro* in microsomes isolated from thyroids was markedly higher for the monkeys (4.1×10^{-6} mol/L) than for rats (8.1×10^{-8} mol/L) (Takayama *et al.*, 1986). These findings suggest that rats are more sensitive to the anti-thyroid effects of propyl-

thiouracil than primates and that inhibition of thyroid peroxidase plays an important role in the anti-thyroid effect of propylthiouracil.

Male Sprague-Dawley rats given 0.05% propylthiouracil in the drinking-water for 17 days showed a decreased (40%) proportion of suppressor T cells in the spleen (Pacini *et al*., 1983).

Intraperitoneal administration of propylthiouracil at 0.5–1.5 mmol/kg bw (85–255 mg/kg bw) to male Sprague-Dawley rats resulted in dose-related decreases in body and spleen weight and an increase in liver weight. Leukocyte counts were markedly reduced. Histologically, congestion of red pulp in the spleen and vacuolization of the liver were noted (Kariya *et al*., 1983).

Female Fischer 344 rats were given 0.1% propylthiouracil in the drinking-water for 3, 7, 14 or 28 days and observed 3, 7 and 14 days after cessation of treatment. During propylthiouracil ingestion, growth hormone-producing cells in the pituitary gland lost their secretory granules, became enlarged and displayed progressive dilatation of rough endoplasmic reticulum, becoming thyroidectomy cells. This effect was reversible: 14 days after treatment ceased, the normal pituitary structure was seen (Horvath *et al*., 1990).

Young (3 months) and aged (26 months) male Lewis rats were given drinking-water containing 0.05% propylthiouracil for 4 weeks. In the younger animals, propylthiouracil increased the percentage of sphingomyelin in synaptosomes from the cerebral cortex. In contrast, a decrease in glycerophosphocholine concentration and an increase in that of cholesterol were noted in aged rats (Salvati *et al*., 1994).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

A review of the clinical literature resulted in limited information on the risk of propylthiouracil-induced malformations in newborns, but the authors noted that an estimated 1–5% of women treated with propylthiouracil during pregnancy have infants who develop significant transient hypothyroidism (Friedman & Polifka, 1994).

Neonatal goitre was observed in one of a dizygotic set of twins whose mother had received propylthiouracil during pregnancy at an initial dose of 400 mg/day, which was subsequently reduced to 100 mg/day. The reason for the apparently selective effect of propylthiouracil on one of the twins was not clear. The goitre receded within 2 weeks, without therapy (Refetoff *et al*., 1974).

In 20 women who had received propylthiouracil during the third trimester of pregnancy at doses of 50–400 mg/day, four cases of neonatal goitre, one of thyrotoxicosis, three pregnancy losses and two malformations occurred (Mujtaba & Burrow, 1975). [The Working Group noted that many of these outcomes may have been related to the underlying condition.] In a follow-up study, the intellectual capacity of 18 children whose mothers received propylthiouracil during pregnancy was compared

with that of 17 siblings who had not been exposed. The two groups did not differ in a standard intelligence test, the Peabody test, the Goodenough test or on a number of physical characteristics (Burrow *et al*., 1968). Similarly, no differences were noted in the distribution of IQs in a group of 28 children who had been exposed to propylthiouracil *in utero* (23 exposed at least in the third trimester) due to treatment of maternal Graves disease and in 32 unexposed siblings (Burrow *et al*., 1978).

In six pregnant hyperthyroid women who received a daily oral dose of 50, 100 or 150 mg of propylthiouracil, a significant inverse correlation ($r = –0.92$; $p = 0.026$) was found between the area under the curve for concentration–time for maternal serum propylthiouracil in the third trimester and the index of free T4 in cord serum (Gardner *et al*., 1986).

In a study of 34 women with Graves hyperthyroidism who received propylthiouracil during pregnancy, 6% (2/34) of cord blood samples contained free T4 at concentrations below the normal range, while 21% (7/34) had concentrations of TSH above the normal range. All the infants with low free T4 or high TSH concentrations were clinically euthyroid and none had goitre at birth (Momotani *et al*., 1997).

Transient neonatal hypothyroidism was seen in the offspring of 11 women who had received propylthiouracil at a dose of 100–200 mg/day at term [route unspecified] for Graves disease during pregnancy. The controls were 40 infants born around the same time. The free and total serum T4 concentrations, but not that of T3, were significantly lower in the exposed infants 1 and 3 days after birth (Cheron *et al*., 1981).

4.3.2 *Experimental systems*

Testicular growth and serum testosterone concentrations were studied in groups of 8–24 male offspring at 90, 135, 160 and 180 days of age after administration of propylthiouracil in the drinking-water at 0.1% w/v to their lactating Sprague-Dawley dams from the day of parturition until day 25. The growth of treated offspring was reduced up to 25 days of age and then generally paralleled that of control animals, but their body weight remained lower than that of the controls. At all ages studied, the testis weights were increased in the propylthiouracil-exposed groups, despite reductions in body weights. For example, at 90 days of age, the testis weight was increased by 41%, while the body weight was reduced by 22%. Histologically, there was evidence of enhancement of normal spermatogenesis. Epididymal, seminal vesicle and ventral prostate weights were also increased, but this effect was not apparent until 135 days of age. The weights of non-reproductive organs (e.g. brain, liver, pituitary and salivary glands) were reduced in the exposed groups. There was no effect on serum T4, T3 or testosterone concentration at any adult age, and there were no obvious histological changes in any tissue. Administration of T4 at 15 µg/kg bw per day and T3 at 10 µg/kg bw per day to pups during exposure to propylthiouracil abolished the effects on testicular growth (Cooke & Meisami, 1991). A subsequent study showed an increase in daily sperm production of 83–136%, depending on age (Cooke *et al*., 1991). The

increases in testis weight and daily sperm production could not be induced by prenatal exposure to propylthiouracil (gestation day 16 to birth) or by exposure beginning after postnatal day 8 (Cooke *et al.*, 1992). While the serum testosterone concentration was not permanently affected by this treatment, the circulating gonadotropin concentration remained 30–50% lower than that in controls throughout adulthood, an effect related to impairment of gonadal feedback and gonadotrope synthetic ability (Kirby *et al.*, 1997). These results suggest a direct impairment of gonadotropin-releasing hormone regulation of gonadotrope development.

Of six interstitial cell types, only Leydig cells showed an increased mitotic labelling index in male pups of rat dams given propylthiouracil at 0.1% in the drinking-water from the day of parturition to the time of weaning 24 days *post partum* (Hardy *et al.*, 1996). The total number of Leydig cells in the testes of 180-day-old male offspring of dams given propylthiouracil at 0.1% in the drinking-water for the first 25 days of their life was increased by about 70%, while luteinizing hormone-stimulated testosterone production and the steroidogenic potential from 22(*R*)-hydroxycholesterol — measured as testosterone production — were reduced by 55% and 73%, respectively (Hardy *et al.*, 1993). A similar doubling of the number of Leydig cells was reported in 135-day-old male Sprague-Dawley rats made hypothyroid by the addition of 0.1% propylthiouracil to the drinking-water of their dams from parturition through postnatal day 25, in contrast to a lower average volume and steroid production per Leydig cell (Mendis-Handagama & Sharma, 1994). Examination of 1-, 7-, 14- and 21-day-old male rats exposed to 0.1% propylthiouracil in their dams' drinking-water showed that, while the number of fetal Leydig cells did not differ from that in controls at any age, there was a delay in the appearance of adult-type Leydig cells (11β-hydroxysteroid dehydrogenase-positive cells) at day 21. In parallel with the morphological delay, luteinizing hormone-stimulated androstenedione production from testis *in vitro* increased from day 14 to day 21 in samples from controls but not in those from propylthiouracil-treated rats (Mendis-Handagama *et al.*, 1998). A decrease in the relative proportion of Leydig cells (identified by morphology and 3β-hydroxysteroid dehydrogenase staining) in interstitial cells were also observed between day 12 and day 16 in propylthiouracil-exposed Wistar rats (Teerds *et al.*, 1998).

Ultrastructural analysis of Sertoli cells provided evidence of an approximate 10-day delay in development in 25-day-old propylthiouracil-treated male rats, including the presence of mitotic Sertoli cells not present in 25-day-old control males (De Franca *et al.*, 1995). The observed effects on Sertoli cell development confirmed earlier work in Wistar rats exposed to 0.1% propylthiouracil in the drinking-water from birth through day 26. The authors found a cessation of proliferation of control Sertoli cells by day 20, as measured by a bromodeoxyuridine-labelling index, whereas propylthiouracil-treated animals had significantly enhanced labelling indices beginning on day 12 and continuing through at least day 26. As a result, there was an 84% increase in the number of Sertoli cells by day 36 (Van Haaster *et al.*, 1992).

In parallel with the delays in Leydig and Sertoli cell development, the development of germ cells was also impaired by neonatal exposure to propylthiouracil. When Sprague-Dawley rats were given 0.1% propylthiouracil in the drinking-water on days 1–25 of postnatal life, decreases in the numbers of spermatocytes and round spermatids were observed at days 20 and 30 in the testes of propylthiouracil-treated rats when compared with controls (Simorangkir *et al*., 1997).

Further examination of this experimental model of increased testis weight and function after exposure of rats to propylthiouracil during days 1–24 of life indicated that the testis weights were reduced between 10 and 60 days of age, after which time the increase became apparent (Kirby *et al*., 1992). Serum luteinizing and follicle-stimulating hormone concentrations were reduced to 50–70% of control levels throughout life, the changes being noticeable early after onset of exposure to propylthiouracil. The serum concentrations of growth hormone, prolactin and T4, which were depressed during exposure, returned to control levels at 40–50 days of age — i.e. within a few weeks after cessation of treatment — as did the increase in TSH concentration. The dose–response characteristics of the effect on testes were evaluated in 90-day-old male rats given 0, 0.0004, 0.0015, 0.006, 0.012 or 0.1% propylthiouracil in their drinking-water from birth to postnatal day 25. Both testis weight and daily sperm production were significantly increased at all concentrations. The testis weight reached a plateau and the daily sperm production a peak value at the 0.006% concentration. Maternal water consumption was significantly reduced at 0.1% propylthiouracil during days 1–13 *post partum* and only slightly reduced at 0.006% (Cooke *et al.*, 1993).

Overall, these data support the conclusion that neonatal hypothyroidism in rats allows a prolonged period of proliferation of Sertoli cells, which ultimately leads to increased numbers of Leydig cells, increased testis weights and increased daily sperm production in adults. While most of the studies were conducted by giving drinking-water containing 0.1% propylthiouracil on days 1–25 of postnatal life, one study suggested that the effects would probably occur at concentrations down to at least 0.0004% propylthiouracil in water.

In order to study the effects of propylthiouracil on prostate weight, the offspring of Sprague-Dawley rats maintained on 0.1% propylthiouracil in the drinking-water from parturition until they were 25 days of age were examined between days 14 and 180. The ventral prostate weights were lower than those of controls up to 95 days of age but increased from day 95, and the glands were about 40% heavier at 180 days of age. The increase in weight was at least partially due to the presence of new ductal structures. The histological appearance of the prostate was normal at all ages, but a transient increase in amiloride-inhibitable plasminogen activator activity was seen in the ventral and dorso-lateral prostate at 42 days of age. These activities had returned to control levels by 90 days. Treatment with propylthiouracil also increased the activity of metalloprotease in the ventral prostate at 21–42 days of age. and in the dorso-lateral prostate at 21 and 28 days of age (Wilson *et al*., 1997).

Examination of female Wistar rats that received 0.1% propylthiouracil in the drinking-water from birth through day 40 indicated that their body weights were significantly reduced by 12 days of age and their ovarian weights by 21 days of age; by day 40, there were signs of altered follicular development. In contrast to effects seen in males, the follicle-stimulating hormone concentration was not reduced in propylthiouracil-treated females (Dijkstra *et al*., 1996).

Groups of 70–114-day-old female Sprague-Dawley rats were exposed to propylthiouracil in the diet (0.3%) and drinking-water (0.001%) from parturition until their pups were 30 days of age. There were four litters per group. The serum T4 concentrations of the dams were depressed through 120 days of age, and their body weight was diminished by about 20%. Neuroanatomical effects in 90-day-old offspring of treated dams included thinning of the cerebellar cortex and fewer synapses in Purkinje cells. In behavioural assessments which included differential reinforcement of low-rate learning, escape and avoidance tasks and motor activity and exploration, control rats learned the escape and avoidance tasks faster and were hyperactive (Schalock *et al*., 1977).

The effects of propylthiouracil on heart and kidney development were studied in Sprague-Dawley rats by treating their dams by subcutaneous injection of 20 mg/kg bw from gestation day 17 to lactation day 5, and by direct injection of the pups on postnatal days 1–5. Body and organ weights and organ DNA and protein content were determined in groups of 7–12 animals on multiple days between birth and day 50. Propylthiouracil significantly impaired body growth and heart and kidney weights (by 10–25%), although the weights had returned to control levels by 50 days of age. The changes in the DNA content of these two organs were similar to the body weight effects, recovery taking longer in the kidney than in the heart; cell size was reduced to a greater extent and for longer periods than cell number (Slotkin *et al*., 1992).

Coronary arterioles were examined in 12-, 28- and 80-day-old Sprague-Dawley rats of dams that had received 0.05% propylthiouracil in their drinking-water on postnatal days 2–28. The body weights of the offspring were significantly depressed after day 20, while their heart rates were significantly depressed at 12 and 28 days of age. Long-term depression of the cardiac mass was also noted, in the presence of capillary proliferation and marked attenuation of arteriolar growth (Heron & Rakusan, 1996).

Female Wistar rats received 0.1% propylthiouracil in the drinking-water from the beginning of gestation through lactation [precise treatment period not indicated], and brain development was evaluated in 6–10 offspring per group on postnatal days 5, 20 and 48. Propylthiouracil significantly reduced the live litter size and pup weight at all ages and also significantly reduced the volume of the neocortex. Further analysis indicated reduced numbers of glial cells in the neocortex only at day 48, while the numbers of neurons were not significantly reduced at any age (Behnam-Rassoli *et al*., 1991).

The auditory response (brainstem-response audiometry) to frequencies of 4 and 16 kHz was evaluated in Sprague-Dawley rats 12, 16, 25 and 125 days of age that had been exposed to propylthiouracil during various 10-day periods of development. For

exposure during gestation, 0.05% propylthiouracil was given in the drinking-water; for exposure after birth, 7 mg/kg bw were given by subcutaneous injection. Hypothyrodism was confirmed by a hormone assay. After neonatal exposure, the concentrations of thyroid hormones were reduced to about 20% of the control levels and that of TSH was about 10-fold higher. The hormone concentrations were not significantly reduced when exposure began at 28 or 120 days of age. Treatment with propylthiouracil significantly increased the latency of wave 1 (representing the cochlear nerve compound action potential) of the brainstem response when given from 3 days before parturition through 6 days of age, but had no permanent effect when given for 10 days starting 10 days after birth (Hébert *et al.*, 1985).

The effects of propylthiouracil on growth, motor development and auditory function were evaluated in Long Evans rats (six to eight litters per group) exposed via the drinking-water to propylthiouracil at 0, 1, 5 or 25 mg/L from gestation day 18 to postnatal day 21. No effects were observed at 1 mg/L. At 5 and 25 mg/L, the serum T4 concentration was sharply reduced on days 1, 7, 14 and 21 after birth, while that of T3 was reduced on days 7, 14 and 21 at 25 mg/L and on day 21 at 5 mg/L. Pups exposed to 25 mg/L had reduced body weights, delayed eye opening, delayed preweaning motor activity and persistent postweaning hyperactivity. Slight effects on eye opening and motor activity were noted at 5 mg/L. Adult offspring that had been exposed to 5 or 25 mg/L showed auditory startle deficits at all frequencies tested (range, 1–40 kHz) (Goldey *et al.*, 1995).

Reproductive development was studied after subcutaneous injection of 0 or 50 mg/kg bw per day propylthiouracil to groups of 10–15 ICR mice from postnatal day 1 until day 28. No effects on growth were seen in the offspring. The plasma T3 concentration was reduced by 40–50% [period not stated]. Histologically, the ovaries of propylthiouracil-treated females showed decreased numbers of primordial, multilaminar and Graafian follicles as folliculogenesis occurred during days 14–28. In males, there was evidence of reduced numbers of seminiferous tubules, but the histological appearance was normal. The fertility of both male and female treated mice was normal (Chan & Ng, 1995).

Daily exposure by oral gavage to propylthiouracil at 0 or 50 mg/kg bw of groups of six male and female CD rats on days 26–96 affected the growth rates of animals of each sex, altered the estrous cycles of females (with a predominance of diestrous stages), increased the weights of the thyroid, pituitary and testis and decreased the weight of the adrenals (Baksi, 1973).

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*

Hepatic and renal 5′-deiodinase activities were strongly inhibited in microsomal preparations from male Sprague-Dawley rats that had been given propylthiouracil orally at 10 mg/kg bw per day for 7 or 14 days (de Sandro *et al*., 1991). The inhibition could be reversed by increasing amounts of glutathione (Yamada *et al*., 1981).

Propylthiouracil significantly decreased cytochrome *c* reductase and aniline hydroxylase activity in male Wistar rat microsomes (Raheja *et al*., 1985).

Propylthiouracil inhibited glutathione transferases in a concentration-dependent manner, a 10-mmol/L concentration causing 25% inhibition. The *S*-oxides of propylthiouracil were even more potent inhibitors: the 2-sulfonate inhibited the enzyme activity by 80% (Kariya *et al*., 1986).

Propylthiouracil given at 0.05% in drinking-water for 4 weeks to young and aged male Lewis rats (3 and 26 months, respectively) resulted in increased synaptosomal acetylcholinesterase activity in both groups, an increased density of muscarinic receptor sites in the young rats and an increase in synaptosomal cholesterol concentration in the aged animals (Salvati *et al*., 1994).

Propylthiouracil increased thyroglobulin mRNA levels in the Fischer rat thyroid cell line FRTL-5 and resulted in accumulation of thyroglobulin in the medium. The total RNA levels were not affected. The effects were suppressed by iodide and did not occur when protein synthesis was inhibited by cycloheximide (Leer *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)

Propylthiouracil did not induce gene mutations in bacteria, or DNA strand breaks in primary cultures of rat or human hepatocytes. It was marginally mutagenic to yeast. Chromosomal aberrations were not induced in a mouse mammary carcinoma-derived cell line or in cultured thyroid cells [not otherwise defined] derived from male Wistar rats given drinking-water containing propylthiouracil at 0.06 mg/L for 10 or 15 weeks. It did not induce somatic recombination in eye cells of *Drosophila melanogaster* when administered continuously in feed to larvae.

4.6 Mechanistic considerations

There are insufficient data to evaluate the genotoxicity of propylthiouracil.

The main effect of propylthiouracil in humans and rodents is inhibition of thyroid peroxidase, which results in decreased plasma concentrations of T3 and T4 and an

Table 1. Genetic and related effects of propylthiouracil

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli Sd-4-73, reverse mutation	–	NT	NR	Szybalski (1958)
Saccharomyces cerevisiae D6, petite mutation	(+)	NT	1000	Wilkie & Gooneskera (1980)
Drosophila melanogaster, somatic recombination, *w*/*w*+ locus	–		170 µg/mL in feed	Rodriguez-Arnaiz (1998)
DNA damage, rat hepatocytes *in vitro*	–	NT	953	Martelli *et al.* (1992)
Chromosomal aberrations, FM3A mouse mammary carcinoma cell line *in vitro*	–	NT	1073	Kodama *et al*. (1980)
Chromosomal aberrations, Wistar rat thyroid cells *ex vivo*	–	NT	0.06 mg/L in drinking-water, 15 weeks	Speight *et al*. (1968)
DNA damage, human hepatocytes *in vitro*	–	NT	953	Martelli *et al*. (1992)

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

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; NR, not reported

increased concentration of TSH, with consequent thyroid follicular-cell proliferation and growth. Squirrel monkeys are much less sensitive to the effect of propylthiouracil on thyroid peroxidase than rats. Another effect of propylthiouracil is inhibition of conversion of T4 to T3 by inhibiting type-1 deiodinase. Alteration of thyroid hormone production is the presumptive mechanism for thyroid tumour formation in rodents.

The lack of adequate data on genotoxicity for propylthiouracil precludes a conclusion regarding the mechanism of carcinogenicity.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Propylthiouracil is a thionamide anti-thyroid drug that has been widely used since the 1940s 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 propylthiouracil 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

Although no conventional bioassay of carcinogenicity in rodents has been reported, propylthiouracil has produced tumours in multiple species. In two small studies in mice, oral administration of propylthiouracil produced thyroid follicular-cell carcinomas and tumours of the anterior pituitary. In multiple studies with various strains of rats, propylthiouracil produced thyroid follicular-cell adenomas and carcinomas. In single studies, propylthiouracil produced thyroid follicular-cell adenomas and carcinomas in hamsters and adenomas in guinea-pigs. In initiation–promotion models of thyroid carcinogenesis

in rats, propylthiouracil increased the incidence of thyroid follicular-cell tumours initiated by *N*-methyl-*N*-nitrosourea or *N*-nitrosobis(2-hydroxypropyl)amine.

5.4 Other relevant data

The elimination of propylthiouracil in both humans and experimental animals is relatively rapid, and the major metabolic pathway is glucuronidation and excretion in the urine.

The main effect of propylthiouracil in humans and rodents is interference with thyroid peroxidase-mediated iodination of thyroglobulin, which results in decreased plasma concentrations of triiodothyronine and thyroxine and increases in those of thyroid-stimulating hormone, with consequent thyroid follicular-cell proliferation and thyroid growth. This is a plausible mechanism of propylthiouracil-induced tumorigenesis in the thyroid.

Propylthiouracil is not considered to be a human teratogen, although a small percentage of infants whose mothers received the drug during pregnancy developed transient hypothyroidism. Follow-up of small numbers of offspring exposed prenatally did not suggest impairment of intellectual development. Experimental studies on the effects of propylthiouracil focused on the consequences of the induction of hypothyroidism during the early postnatal period on the development and functioning of the brain and reproductive tract. Hyperactivity, auditory deficits and increased sperm production have been observed in rats. The latter outcome is the result of a prolonged period of proliferation of Sertoli cells, and subsequently Leydig cells, in the testes that allows additional spermatogonia in adulthood.

Propylthiouracil has not been adequately tested for gene mutation induction. It did not induce mutations in bacteria, and it was only marginally mutagenic in yeast. Propylthiouracil did not induce chromosomal recombination in insects, DNA strand breaks in rat or human hepatocytes or chromosomal aberrations in a mouse mammary carcinoma-derived cell line. It did not induce chromosomal aberrations in thyroid cells of rats exposed *in vivo* via the drinking-water.

5.5 Evaluation

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

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

Overall evaluation

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

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