GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

This seventy-ninth volume of *IARC Monographs* contains evaluations of the carcinogenic risk to humans of 19 chemicals that have produced thyroid tumours in rodents. Unless otherwise stated, the term 'thyroid tumour', as used in this volume, refers to neoplasms of thyroid follicular cell origin.

These substances have diverse uses. A number are used as drugs, including so-called 'anti-thyroid' agents (methimazole, methylthiouracil, propylthiouracil and thiouracil), sedatives (doxylamine succinate and phenobarbital), antifungal agents (griseofulvin), diuretics (spironolactone) and antibacterial agents (sulfamethazine and sulfamethoxazole). The others are or have been used in agriculture as pesticides (amitrole, chlordane, heptachlor, hexachlorobenzene and toxaphene), in foods or cosmetics (kojic acid), in hair dyes (2,4-diaminoanisole) and as industrial chemicals (*N*,*N*′-diethylthiourea, ethylenethiourea, and thiourea). Many of these agents have been evaluated previously in *IARC Monographs*, but some (*N*,*N*′-diethylthiourea, doxylamine succinate, kojic acid, methimazole and sulfamethazine) are evaluated for the first time.

Since the previous evaluations of these agents in the *Monographs* series, new data, particularly on mechanisms, have become available. Such data now play an important role in making overall evaluations of carcinogenicity to humans (Vainio *et al*., 1992). A number of guidelines have been developed for the use of information on the mechanisms of induction of tumours of the kidney, urinary bladder and thyroid gland in rodents in making IARC evaluations (Capen *et al*., 1999), and these guidelines were used in the present volume.

Use of anti-thyroid drugs in humans

Thioureylene anti-thyroid drugs belong to the family of thionamides, which are heterocyclic thiourea derivatives that potently inhibit thyroid hormone synthesis. They were developed in the mid-1940s to early 1950s on the basis of observations that thiourea and thiocarbamide are goitrogenic in animals. Thiouracil was the first 'anti-thyroid drug' to be used clinically, but its use was short-lived because of toxicity and because other, more active drugs (i.e. propylthiouracil, methylthiouracil and methimazole) were soon developed (Astwood & VaanderLaan, 1945; Stanley & Astwood, 1949). In addition to propylthiouracil and methimazole, the 3-carbethoxy derivative of methimazole,

carbimazole, is widely used in Europe and Asia. Carbimazole is metabolized *in vivo* to methimazole, which exerts the anti-thyroid effects. It has been estimated that 0.1–0.3% of the population in a number of developed countries is taking antithyroid drugs at any given time (Anon., 1988).

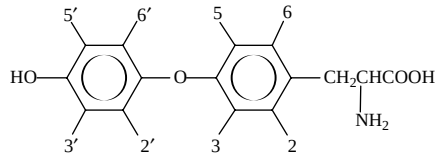
The mechanism of action of thioureylene anti-thyroid drugs is still not completely understood. The drugs are actively concentrated by the thyroid gland. They act to block the formation of thyroid hormone by inhibiting two key steps in intrathyroidal hormone synthesis: (i) incorporation of oxidized iodine into tyrosine residues in thyroglobulin to form iodotyrosines (the so-called 'organification' step), and (ii) the 'coupling reaction', wherein iodotyrosine residues within the thyroglobulin molecule couple to form the iodothyronines, thyroxine (T4) and triiodothyronine (T3) (Taurog, 1976) (see Figure 1). The organification step is catalysed by the haem-containing glycoprotein enzyme thyroid peroxidase (TPO), which provides a haem-bound oxidized iodine moiety (TPO-I^+). Although antithyroid drugs are potent inhibitors of TPO *in vitro*, their mechanism of action *in vivo* is more complex. It now appears that, within the thyroid gland, the drugs themselves serve as TPO substrates. Upon entry into the thyroid, they are iodinated and thus act as TPO competitors by diverting the oxidized iodine species (TPO-I^+) away from the organification process (Davidson *et al.*, 1978; Engler *et al.*, 1982). The inhibitory effects of antithyroid drugs on the coupling process are less well characterized but also probably involve interference with TPO (Cooper, 2000).

Anti-thyroid drugs may have other, less well-documented intrathyroidal effects. There is evidence that they can interfere with thyroglobulin synthesis (Monaco *et al.*, 1980) and possibly with the thyroglobulin structure (Papapetrou *et al.*, 1975), but the clinical significance of these observations is uncertain. The drugs have no effect on iodine trapping by the thyroid, nor do they interfere with thyroid hormone secretion by the gland.

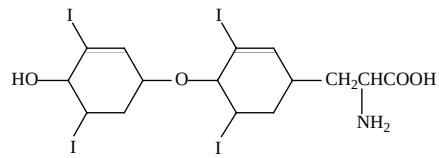
In addition to these intrathyroidal effects that relate to thyroid hormone synthesis, the drugs also have potentially clinically important extrathyroidal effects. The first is the inhibition by propylthiouracil (but not methimazole) of 5′-deiodinase type I, the enzyme that catalyses the conversion of T4 to T3 in peripheral tissues. T3 is the biologically active form of thyroid hormone and, since 80% of daily T3 production arises from peripheral T4 deiodination rather than from direct glandular secretion, inhibition of this enzyme by propylthiouracil causes an immediate decrease in serum T3 concentrations (Cooper *et al.*, 1982). However, this effect probably does not confer a clinical advantage of propylthiouracil over methimazole, except in severe thyrotoxicosis ('thyroid storm'). The second extrathyroidal effect relates to possible effects on the immune system. Graves disease, the commonest cause of hyperthyroidism by far, is an autoimmune disease. Numerous in-vitro and in-vivo studies (summarized by Cooper, 1998) have suggested that the thionamide anti-thyroid drugs have immunosuppressive effects, and it is these effects that are thought to be responsible for the remissions that are seen in anywhere from 20 to 80% of patients after a 12–24-month course of drug therapy. However, it is also possible that anti-thyroid drugs simply control the hyperthyroid state

Figure 1. Thyronine, thyroid hormones and precursors

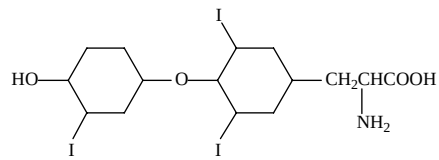
Thyronine



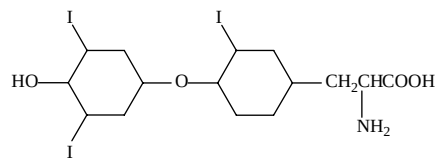
Thyroxine (= T_4)



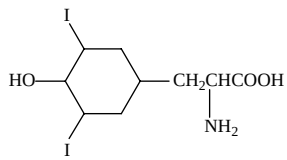
3,5,3′-Triiodothyronine (= T_3)



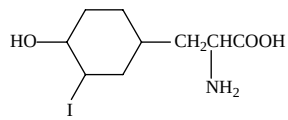
3,3′,5′-Triiodothyronine (= rT_3)



Diiodotyrosine



Iodotyrosine



From Hardman *et al.* (1995)

by permitting the disordered immune system to return to normal after correction of thyroid hormone concentrations in the blood (Cooper, 1998).

At present, the only clinical use of the thionamide anti-thyroid drugs is in the treatment of hyperthyroidism caused by Graves disease, toxic thyroid nodules, toxic multinodular goitre and several other rare causes of hyperthyroidism. In patients with Graves disease, anti-thyroid drugs are used in two contexts. In some patients, they are given for several months to normalize thyroid function prior to definitive therapy with either radioiodine or surgery. In other patients, they are given for 1–2 years, in the hope that the patient will enter a period of remission.

Thyroid cancer in humans

In humans, thyroid cancer is relatively rare. The great majority of thyroid cancers arise from the epithelial elements of the gland, mostly from the follicular cells (Robbins *et al*., 1984). Thyroid carcinomas fall into two broad groups: differentiated and undifferentiated (anaplastic). The former group is subdivided into two types, papillary and follicular. Medullary carcinoma derives from parafollicular cells (i.e. calcitonin-producing cells, or C-cells) and accounts for 5–15% of most series of thyroid carcinomas (Franceschi *et al*., 1993). The etiology of this type is separate from those of other thyroid carcinomas, inheritance being an important determinant (Ron, 1996).

Thyroid carcinomas vary widely in the degree of malignancy, ranging from relatively benign to rapidly fatal. The difference depends almost entirely on the histological type. A 'pool' of individuals with occult thyroid carcinomas (mostly of the papillary type) is probably present in most populations, even among young people. Large differences in the estimated frequency of cancer at this site can therefore be due to variation in diagnostic intensity. Data on changing trends of incidence and mortality are thus subject to reservation, depending on the degree to which they have been influenced by changing diagnostic criteria and the precision of histopathological description.

Mortality rates from thyroid cancer have decreased in most developed countries, and the decreases have been especially marked in Austria, Iceland and Switzerland, where the rates were relatively elevated in the early 1990s (i.e. approximately 2/100 000 compared to < 1/100 000 nearly everywhere else). Mortality rates have also decreased in the United Kingdom and the USA. Upward trends in the incidence of thyroid cancer were recorded in most developed countries at least up to the 1970s or early 1980s, with stabilization thereafter (Franceschi *et al.*, 1993). Thyroid cancer shows a two- to threefold higher incidence in women than in men.

Thyroid function is regulated by pituitary (thyroid-stimulating hormone; TSH) and hypothalamic (thyrotropin-releasing hormone) mediators and by the glandular organic iodine content. The role of elevated TSH concentrations in the pathogenesis of thyroid cancer in humans is unclear, as epidemiological studies have shown excess incidences of thyroid cancer in both iodine-rich and iodine-deficient areas, and both iodine

deficiency and iodine excess may enhance TSH secretion. Endemic goitre due to iodine excess has been demonstrated among fishermen in Japan (Suzuki *et al*., 1965; Okamura *et al*., 1987) and Norway (Jorgensen & Svindland, 1991) who eat large quantities of iodine-rich seaweed, and in persons living in areas in China where the iodine concentration in the drinking-water is very high (Li *et al*., 1987) and where large quantities of iodine-rich salt or pickled vegetables (Zhu *et al*., 1984) are ingested. Papillary carcinomas of the thyroid represent the vast majority of thyroid cancers in iodine-sufficient areas, whereas follicular and anaplastic carcinomas occur more frequently in iodine-deficient areas (Williams *et al*., 1977).

Few epidemiological data are available on the relationship between thyroid cancer and TSH concentrations. Only one study provided information on TSH concentrations in serum during the preclinical phase of thyroid cancer. In this study, sera were available for 43 patients with thyroid cancer and 128 healthy controls, which had been collected on average 4 years earlier in a large Norwegian serum bank. No difference in TSH concentration was found, whereas higher concentrations of thyroid-binding globulin were measured in the sera of thyroid cancer patients than in those of controls. The increase in thyroid-binding globulin was interpreted as representing either secretion from a slowly growing, subclinical tumour or leakage from normal follicles (Thoresen *et al*., 1988).

Only two case–control studies have provided data on the risk for thyroid cancer in relation to residence in areas endemic for goitre. In an Italian study, the relative risk for having resided in such an area was 1.3 for < 20 years of residence and 1.6 for 20 or more years (D'Avanzo *et al*., 1995). In a study in Sweden, a trend towards an association was found with duration of residence in areas endemic for goitre (Galanti *et al*., 1995).

The results are far more consistent with respect to the role of previous benign thyroid disease. In a re-analysis of the data from 12 case–control studies in Asia, Europe and the USA, involving a total of 2094 women and 425 men with cancer of the thyroid and 3248 female and 928 male controls, persons with a history of benign thyroid nodules or adenomas had a high risk for thyroid cancer (odds ratio, 30; 95% confidence interval [CI], 15–62 for women; 18 cases versus 0 controls in men). The pooled odds ratios associated with a history of goitre were 5.9 (95% CI, 4.2–8.1) for women and 38 (95% CI, 5.0–291) for men, whereas a history of hypothyroidism or hyperthyroidism was not significantly associated with risk. The excess risk associated with benign nodules or adenomas and goitre was greatest within 2–4 years before diagnosis of thyroid cancer, but an elevated odds ratio was present 10 years or more before diagnosis of cancer (Franceschi *et al*., 1999).

Most thyroid disorders, including cancer, are several times more prevalent in women than in men, which indicates a possible role of female hormones (Franceschi *et al*., 1993). In a pooled analysis of 14 case–control studies (2247 female cases of thyroid cancer and 3699 controls), however, parity and a history of spontaneous or induced abortions or infertility were not associated with risk. The odds ratio was above unity

for women who had first given birth at a late age (1.1; 95% CI, 1.0–1.3 for a 5-year delay) (Negri *et al*., 1999). The odds ratio was significantly increased for women who were currently using oral contraceptives (odds ratio, 1.5; 95% CI, 1.0–2.1) but declined with increasing time since cessation of use (La Vecchia *et al*., 1999). The moderate excess risk among current users of oral contraceptives, if not due to increased surveillance for thyroid masses among such users, is similar to that described for breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 1996) and would imply a role of female hormones in the promotion of thyroid cancer.

Ionizing radiation is the only well-defined risk factor for thyroid carcinoma. A pooled analysis of five cohort studies and two case–control investigations, cumulating over 3 000 000 person–years of follow-up and 700 thyroid cancers, showed that, for persons exposed to radiation before the age of 15 years, the dose–response relationship was best described by a linear equation, even down to very low doses (0.10 Gy) (Ron *et al*., 1995). The epidemic of thyroid carcinoma in children exposed to radioiodines as a result of the Chernobyl nuclear reactor accident in 1986 was described in a previous monograph (IARC, 2001).

Epidemiological data on thyroid carcinoma unrelated to exposure to ionizing radiation are scanty. The few studies available generally did not address the specific compounds included in this volume. For example, one cohort study and two case–control studies were carried out among patients receiving anti-thyroid drugs, the identity of which was not specified. These reports are reviewed in each of the four monographs dealing with these drugs (methimazole, methylthiouracil, propylthiouracil and thiouracil). Some compounds (e.g. phenobarbital, chlordane and hexachlorobenzene) have been studied in relation to other cancers. Exposure to non-radioactive chemicals has not been shown to result in the development of thyroid carcinoma in humans.

Pathogenesis of thyroid neoplasms in humans

Studies on the pathogenesis of thyroid neoplasms in humans have tended to focus on structural changes in cancer-related genes in thyroid tumours, rather than on hormonal factors. Most of the work involved molecular studies of human tumours for which no cause was determined, but in some cases the development of a well-differentiated carcinoma has been strongly correlated with a history of exposure to external radiation or to iodine deficiency.

Chromosomal abnormalities have been identified in follicular and papillary thyroid adenomas and carcinomas and in medullary thyroid neoplasms (Gillenwater & Weber, 1997; Kroll *et al*., 2000), as well as in mixed medullary-follicular carcinomas (Volante *et al*., 1999). These chromosomal changes are associated with alterations in both oncogenes and tumour suppressor genes. Considerable research has focused on the *met*, *ras* and *ret* proto-oncogenes and on chimaeric oncogenes, such as the newly identified *PAX8-PPARγ1* fusion oncogene (Kroll *et al.*, 2000). Later-stage mutational events in

thyroid carcinogenesis may involve mutations in *p53*. Mutated oncogenes are found in 15–70% of thyroid carcinomas, depending on the tumour type (Gillenwater & Weber, 1997; Lazzereschi *et al.*, 1997).

Many of the genetic changes that have been identified in human thyroid tumours arise relatively early in tumorigenesis. They indicate the involvement of multiple genetic pathways, some of which are important to thyroid function, e.g. by altering the TSH receptor and its associated signal transducers (reviewed by Suarez, 2000). Constitutive activation of the TSH receptor signal cascade is responsible for the hyperfunctional state of 25–30% of thyroid follicular toxic adenomas and hyperfunctioning tumours (Suarez, 2000).

Thyroid tumours in experimental animals

The background, naturally occurring or 'spontaneous' rate of thyroid follicular-cell tumours in rodents has been reported to be low (Huff, 1999). Among more than 1300 control male and female B6C3F_1 mice and Fischer 344 rats used in assays conducted within the National Toxicology Program in the USA, the frequency was about 2% in male and female mice and male rats and 1% in female rats (range, 0–8%).

In contrast to the general lack of evidence for a role of environmental carcinogens other than ionizing radiation in thyroid carcinogenesis in humans, a large number of chemicals, including genotoxic agents such as *N*-nitrosoalkylureas and *N*-nitrosamines, have produced thyroid tumours in rodents (see Dybing & Sanner, 1999; Huff, 1999; Wilbourn *et al*., 1999). Some of these compounds have genotoxic effects and may also affect TSH; other chemicals that cause thyroid tumours in rats or mice have no detectable genotoxic activity. Such agents often also produce hepatocellular tumours, particularly in mice (see McClain & Rice, 1999). A significant number of pharmaceutical drugs and agricultural chemicals introduced for general use since 1970 cause thyroid follicular cell tumours in rats or mice or both**.** However, as many of the bioassays demonstrating this effect have not been published in the open scientific literature, data on tumours induced by many compounds that might have been chosen for evaluation in this volume were not available.

The lack of evidence for a role of chemicals in the causation of human thyroid neoplasms, in contrast to the frequent observation of thyroid tumours in bioassays for carcinogenicity in experimental animals, raises the question of whether, and in what way, thyroid tumours in laboratory animals predict a cancer hazard for humans (Capen, 1997).

Mechanisms of thyroid follicular-cell proliferation and neoplasia in animals

Little information is available about structural alterations in cancer-related genes in thyroid tumours from rats and mice, in contrast to human thyroid tumours.

There is overwhelming evidence that TSH-induced growth of thyroid epithelial cells plays a critical role in thyroid tumorigenesis in rodents (Thomas & Williams, 1999), whether induced by a carcinogenic chemical or not. Simply feeding an iodine-deficient diet to rats is sufficient to cause not only goitre but thyroid follicular cell adenoma and carcinoma as well (Ohshima & Ward, 1986). The induction of thyroid follicular cell tumours in rats and mice by agents judged to be nongenotoxic is probably primarily a response to dysregulation of the thyroid–pituitary axis of hormonal control of thyroid follicular cell proliferation and function. Prolonged stimulation of the thyroid by TSH, leading to diffuse follicular cell hyperplasia, is an important mechanism in thyroid carcinogenesis in these rodents. Such stimulation can result from decreased synthesis, increased secretion, altered transport and storage or altered metabolism of thyroid hormones (Hard, 1998; Capen *et al*., 1999).

After iodine is taken up in the follicular cell, it is oxidized by thyroid peroxidase and bound to tyrosyl residues of the thyroid-specific protein thyroglobulin. Mono-iodotyrosine and diiodotyrosine are coupled to form T3 and T4, which are released into the circulation where they are bound to plasma proteins (thyroid-binding globulin in humans and albumin in rats). More T4 than T3 is released from the thyroid, but T4 is deiodinated by 5′-monodeiodinase type I peripherally to produce T3 locally. The circulating concentrations of T4 are monitored by the thyrotropic cells of the pituitary, which are responsible for the production of TSH. In the pituitary, T4 is metabolized to T3 by 5′-deiodinase type II, and the T3 then binds to specific receptors in the cell nucleus. A decrease in T3 receptor occupancy results in stimulation of TSH synthesis and secretion.

Xenobiotics can affect thyroid homeostasis by:

- inhibition of iodine uptake by the thyroid (perchlorates, thiocyanates);
- inhibition of thyroid peroxidase and a decrease in iodine utilization (sulfonamides, propylthiouracil, methimazole, thiourea);
- inhibition of T4 or T3 release from the thyroid (lithium, excess iodide);
- increased metabolism of T4 in the liver (phenobarbital, spironolactone, chlordane); and
- inhibition of 5′-monodeiodinase, decreasing conversion of T4 to active T3 in peripheral tissues (propylthiouracil).

If disruption of thyroid function and consequent stimulation of TSH production by the pituitary is sufficiently intense and prolonged, proliferative changes in thyroid follicular epithelium will result, which, in rats and mice, may progress to tumours (Capen, 1997).

Application of mechanistic evidence in evaluations of chemicals that cause thyroid tumours in experimental animals

Criteria for the use of mechanistic data to assess the predictive value of thyroid follicular cell tumours in rodents for evaluating the carcinogenic hazard of chemicals to humans have been described (Capen *et al.*, 1999). These criteria are as follows:

- Agents that lead to the development of thyroid neoplasia through an adaptive physiological mechanism belong to a different category from those that lead to neoplasia through genotoxic mechanisms or through mechanisms involving pathological responses with necrosis and repair.
- Agents that cause thyroid follicular-cell neoplasia in rodents solely through hormonal imbalance can be identified on the basis of the following criteria.
  - No genotoxic activity (agent and/or metabolite) was found in an overall evaluation of the results of tests *in vivo* and *in vitro*.
  - Hormone imbalance was demonstrated under the conditions of the assay for carcinogenicity.
  - The mechanism whereby the agent leads to hormone imbalance has been defined.
- When tumours are observed both in the thyroid and at other sites, they should be evaluated separately on the basis of the modes of action of the agent.
- Agents that induce thyroid follicular-cell tumours in rodents by interfering with thyroid hormone homeostasis can, with some exceptions, notably the sulfonamides, also interfere with thyroid hormone homeostasis in humans if given at a sufficient dose for a sufficient time. These agents can be assumed not to be carcinogenic in humans at concentrations that do not lead to alterations in thyroid hormone homeostasis.

The Working Group considered that some clarification of these criteria was desirable. Specifically, the 'conditions' of the carcinogenicity assay, referred to above, are meant to indicate that hormonal assays and morphological evaluation of the thyroid gland should be carried out in animals of the same species, and preferably the same strain, as were used in the bioassay in which thyroid tumours developed, but not necessarily as part of the bioassay itself. Animals used in hormonal assays should be treated by the same route and dose as animals in which tumours developed in bioassays for carcinogenicity.

Evidence for hormonal imbalance could include measurements of serum thyroid hormone and TSH and of morphological changes characteristic of increased TSH stimulation, including increased thyroid gland weight and diffuse follicular-cell hyperplasia and/or hypertrophy.

General statement regarding the determination of genotoxicity or non-genotoxicity of a substance

There is no general agreement about the numbers or types of tests that are needed to determine the genotoxicity or non-genotoxicity of a substance. It is generally agreed, however, that tests for gene mutation and for chromosomal damage are required (McGregor *et al.*, 1999). The tests for gene mutation most widely used involve bacteria (usually *Salmonella*) and mammalian cells *in vitro*, with and without exogenous metabolic activation. The assays for chromosomal damage include cyto-

genetic analysis *in vitro* or *in vivo* and tests for micronucleus formation *in vitro* and *in vivo*. As a rule, a substance that reproducibly induces gene mutation or chromosomal damage (measured as aberrations or micronuclei) is to be considered a genotoxic agent. It should be specified whether the evidence of genotoxicity is based on the results of in-vitro tests, in-vivo tests or both.

It is more difficult to find agreement on the tests and patterns of test results necessary to declare a substance non-genotoxic. In order to do so, a consistent pattern of negative results should have been found in bacteria and mammalian cells *in vitro* and in mammals *in vivo.*

For most of the agents reviewed in this *Monographs* volume, few data were available from adequate tests of genetic toxicity. The lack of adequate data on genotoxicity precluded application of the above criteria to a number of the substances considered in this volume.

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