I. INTRODUCTION

Several agents, both naturally occurring and man-made, pose the danger of thyroid disease by interfering with thyroid function. These compounds can alter thyroid structure and function by acting directly on the gland or by affecting its regulatory mechanisms. The gland may increase in size to become a goiter. Thyroid hormone secretion may remain adequate or become insufficient depending on dietary iodine intake or the presence of underlying thyroid disease.

Agents and pollutants that cause goiter — also known as environmental goitrogens — will be the focus of this book. The study of environmental goitrogens, requires the understanding, interest, and collaboration of multiple disciplines — some outside the confines of the Biological Sciences. The difficulty in complying with this important requirement has fragmented our knowledge and prevented the effective investigation of many questions that surround this important and controversial issue. With the exception of iodine deficiency, the public health and socioeconomic impact of environmental goitrogens are practically unknown.

II. GENERAL CONSIDERATIONS

A. Compounds Associated with Adverse Effects on the Thyroid

Agents known to have goitrogenic and/or antithyroid effects on the thyroid of humans and other animal species, are listed in Table 1.

B. Physiology and Pathophysiology

To understand the involvement of environmental pollutants in the pathogenesis of thyroid disease, a brief review of thyroid gland physiology is necessary.[1-4] This review, by identifying the site of action and the physiologic mechanisms disrupted by environmental pollutants provides the basis for understanding how such exposure can lead to goitrogenesis with or without hypothyroidism.

1. Agents Acting Directly on the Thyroid

Figure 1 illustrates the three main steps in thyroid gland function. It also lists some environmental pollutants that act directly in the gland by interfering with the process of hormonal synthesis.

The first step involves the active uptake or concentration of inorganic iodide by the thyroid. Environmental goitrogens such as thiocyanate (SCN) interfere with this process. Since SCN has a molecular volume and a charge similar to those of iodide, it competes with iodide for transport in the thyroid cell. The goitrogenic effect of SCN, however, is overcome by iodine administration.

The second step entails the incorporation of oxidized iodine into the amino acid tyrosine — within the peptide sequence of thyroglobulin — to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). These compounds are precursors of the active thyroid hormones, triiodothyronine (T_3), and thyroxine (T_4). This process of organification is mediated by the action of the thyroidal peroxidase enzyme. Resorcinol and its phenolic and phenoliccarboxilic (DHBAs) parent compounds, flavonoids, aliphatic disulfides, and "goitrin", inhibit the process of organification.

The third step consists of the release of the active thyroid hormones, T_3 and T_4, into the circulation. Excess iodide and lithium salts block this step.

Because of their antithyroid effects the administration of any of these agents eventually results in goiter formation, and in some instances in hypothyroidism. For this reason they are called antithyroid or goitrogenic compounds. It becomes apparent that an absolute lack

Table 1
ENVIRONMENTAL AGENTS PRODUCING GOITROGENIC AND/OR ANTITHYROID EFFECTS

Compounds	Goitrogenic/antithyroid effects		
	In vivo		In vitro systems
	Human	Animals	
Sulfurated organics			
Thiocyanate (SCN^-)	+	+	+
Isothiocyanates	NT	+	+
L-5-vinyl-2-thiooxazolidone (goitrin)	+	+	+
Disulfides (R-S-S-R)	NT	+	0, +(?)[a]
Flavonoids (polyphenols)			
Glycosides	NT	+	+
Aglycones	NT	+	+
C-ring fission metabolites (i.e. phloroglucinol, phenolic acids)	NT	+	+
Polyhydroxyphenols and phenol derivatives			
Phenol	NT	NT	+
Catechol (1,2-dihydroxybenzene)	NT	NT	+
Resorcinol (1,3-dihydroxybenzene)	+	+	+
Hydroquinone (1,4-dihydroxybenzene)	NT	NT	+
m-Dihydroxyacetophenones	NT	NT	+
2-Methylresorcinol	NT	+	+
5-Methylresorcinol (orcinol)	NT	+	+
4-Methylcatechol	NT	NT	+
Pyrogallol (1,2,3-trihydroxybenzene)	NT	+	+
Phloroglucinol(1,3,5-trihydroxybenzene)	NT	+	+
4-Chlororesorcinol	NT	+	+
3-Chloro-4-hydroxybenzoic acid	NT	NT	+
2,4-Dinitrophenol	+	+	0
Pyridines			
3-Hydroxypyridine	NT	NT	+
Dihydroxypyridines	NT	+	+
Phthalate esters and metabolites			
Diisobutyl phthalate	NT	NT	0
Dioctyl phthalate	NT	NT	0
o-Phthalic acid	NT	NT	0
m-Phthalic acid	NT	NT	0
3,4-Dihydroxybenzoic acid (DHBA)	NT	NT	+
3,5-Dihydroxybenzoic acid	NT	NT	+
Polychlorinated (PCB) and polybrominated (PBB) biphenyls			
PCBs (Aroclor)	NT	+	NT
PBBs and PBB oxides	+	+	NT
Other organochlorines			
Dichlorodiphenyltrichloroethane (*p,p'*-DDT)	NT	+	NT
Dichlorodiphenyldichloroethane (*p,p'*-DDE) and dieldrin	NT	+	NT
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	NT	+	NT
Polycyclic Aromatic Hydrocarbons (PAH)			
3,4-Benzpyrene (BaP)	NT	+(?)	NT
3-Methylcolanthrene (MCA)	NT	+	NT
7,12-Dimethylbenzanthracene (DMBA)	NT	+	NT
Inorganics			
Excess Iodine	+	+	+
Lithium	+	+	+

Note: + = active; 0 = inactive; and NT = nontested.

[a] = Inactive in TPO assay; Active (?) in thyroid slices assay.

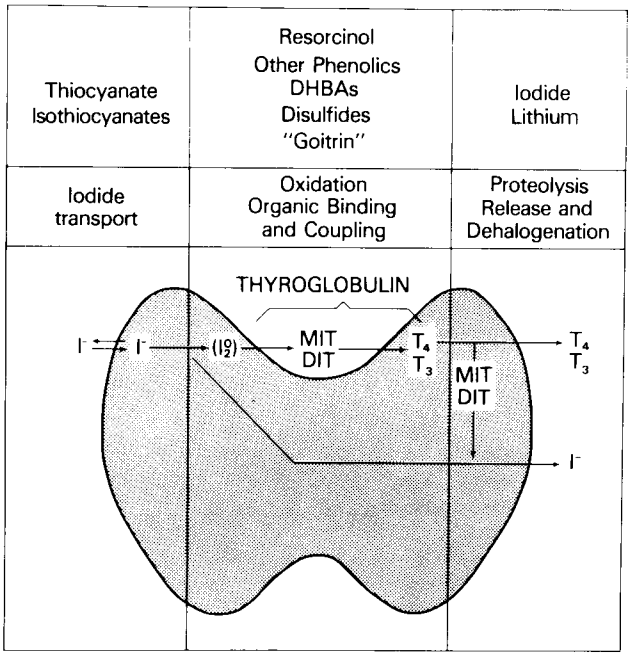

FIGURE 1. Environmental goitrogens and their site of action in the thyroid gland. DHBAs = dihydroxibenzoic acids; I = iodide; MIT = monoiodotyrosine; DIT = diiodotyrosine; T_4 = thyroxine; T_3 = triiodothyronine.[9]

of dietary iodine or a decrease in iodide utilization due to environmental pollutants, or both, can result in "sporadic" or "endemic" goiter.[5]

Thyrotropin (TSH) from the anterior pituitary regulates the rate of synthesis and secretion of thyroid hormones. In turn, T_4 and T_3 act directly on the pituitary to inhibit thyrotropin secretion.[6] Since TSH also exerts a morphogenetic effect on the gland, any increase in thyrotropin secretion which follows exposure to antithyroid compounds would be expected to cause thyroid enlargement. However, the mechanism that induces the trophic changes leading to goiter formation is not well understood.

Furthermore, environmental pollutants operating in genetically predisposed individuals may as well trigger the pathogenic mechanisms that lead to goiter formation and autoimmune thyroiditis. Although this process has been induced experimentally in certain strains of rats, its occurrence in man has not been demonstrated.[7]

2. Agents Acting Indirectly on the Thyroid

A decrease in thyrotropin secretion results in decreased synthesis and release of T_4 and T_3 and involution of the thyroid gland.[8] The antithyroid effect of 2,4-dinitrophenol (DNP) is due in part to an inhibition of the pituitary TSH mechanism. Polymers of the flavonoid, phloretin, also interact with TSH preventing its action at the thyroid cell.[9]

Once T_4 and T_3 are released into the circulation, they are instantaneously bound to serum carrier proteins. DNP interferes also with T_4 binding, further decreasing serum T_4 concentration.[10-12] PCBs exert a similar effect.[13,14]

All circulating T_4 and 20% of T_3 are derived from the thyroid gland. The rest of T_3 is produced by outer ring monodeiodination of T_4 in peripheral tissues. Flavonoids not only inhibit the thyroid peroxidase (TPO), but also the peripheral metabolism of thyroid hormones by acting on iodothyronine deiodinase enzymes.[15,16]

Although deiodination is most important there are two other major pathways for the metabolism and excretion of thyroid hormones. These include the oxidative deamination or transamination of the amino acid residue and the sulfate and glucuronide conjugation of the phenolic ring. In addition to inhibiting the TSH mechanism and interfering with T_4 binding, DNP also accelerates the disappearance of T_4 from the circulation.[10] Thereby, the serum T_4 concentration is lowered even more.

The thyroid hormones, in both free and conjugated forms, are excreted into the intestine along with small amounts of their deiodinated metabolites. Glucuronide conjugation, through the action of a UDP-glucuronyl transferase, occurs primarily in the liver; sulfate conjugation takes place mainly in the kidney by the action of a sulfate transferase. Under normal circumstances, however, little T_4 and T_3 are excreted in the conjugated form.

Polychlorinated biphenyls (PCBs) are potent hepatic microsomal enzyme inducers.[14-17] Investigators have demonstrated that rats exposed to PCBs exhibit a greatly enhanced biliary excretion of circulating T_4. The T_4 is excreted as a glucuronide which is then lost in the feces.[13,14] This response is probably secondary to induction of hepatic microsomal T_4-UDP-glucuronyl transferase. The enhanced peripheral metabolism and reduced binding of T_4 to serum proteins in PCB-treated animals, result in markedly decreased serum T_4 concentrations. These low levels stimulate the pituitary-thyrotropin-thyroid axis and this eventually results in goiter formation. Although PCB-treated animals exhibit decreased serum T_4 their T_3 levels are unchanged. The relative iodine deficiency brought about by the accelerated metabolism of T_4 may induce increased thyroidal T_3 secretion as well as increased peripheral deiodination of T_4 to T_3. Polybrominated biphenyls (PBBs) appear to act similarly to PCBs. There is, however, some indication that they may also interfere directly with the process of hormonal synthesis in the thyroid gland.[18]

In conclusion, environmental pollutants may cause goiter and/or hypothyroidism by acting directly on the thyroid gland or indirectly by altering its regulatory mechanisms and/or the peripheral metabolism and excretion of thyroid hormones.

C. Measurement of Antithyroid and Goitrogenic Activities

The antithyroid and goitrogenic activities of compounds or materials having potential goitrogenicity, can be determined by in vitro and in vivo assays. These methods can be of great help in evaluating the effect of pollutant exposure upon the thyroid gland.

I. In Vitro Assays

A. Inhibition of thyroid peroxidase

Antithyroid substances may suppress thyroid function by lowering the activity of thyroid peroxidase (TPO). TPO catalyzes the oxidation of iodide and subsequent formation of iodotyrosines and thyroid hormones in the thyroid gland. Porcine thyroid peroxidase-catalyzed iodination of bovine serum albumin (BSA) is used to measure the antiperoxidase activity of suspected agents.[19-21]

1. TPO is purified from porcine thyroids[22] and assayed by incubating 6-propylthiouracil (PTU) as the reference standard, experimental compounds or test materials in a phosphate buffer (pH 7.0) at 37°C for 10 min with ^{125}I, BSA, glucose, and glucose oxidase.
2. Protein-bound ^{125}I is separated from free ^{125}I using 0.8 × 15 cm Bio-Gel P-2 (200-400 mesh) columns.
3. The antiperoxidase potency of each compound or test material is represented by the concentration needed to produce 50% inhibition (I_{50}) of control peroxidase activity. Inhibition of TPO is measured at four concentrations and the I_{50} estimated by plotting the concentration of inhibitor versus the TPO activity as percent of control.

B. Inhibition of iodine metabolism in the thyroid

This assay measures three parameters of thyroid function: iodide accumulation (uptake), iodide incorporation into tyrosine to form mono- and diiodotyrosines (MIT and DIT) (iodide oxidation and organification), and finally, coupling of MIT and DIT to form the active thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4). Thyroid (porcine, bovine, rat, etc.) slices, lobes or cell suspensions can be used.[23-26]

1. For instance,[23] a freshly collected porcine thyroid gland is sliced (0.5 mm) and 200-mg portions incubated in Krebs Ringer buffer and 0.5 μCi of ^{125}I for 4 hr at 37°C with either blank control, reference standards, or experimental compounds.
2. Tissue samples are measured for ^{125}I uptake and then homogenized, hydrolized, and lyophilized in preparation for column chromatography. 1 × 1 cm Dowex X8 ion exchange resin columns are used to separate bound ^{125}I from inorganic iodide and 1 × 5 cm Bio-Gel P2 (200 to 400 mesh) columns to separate iodotyrosines (MIT and DIT) from iodothyronines (T_3 and T_4).
3. Antithyroid activities are measured by: (1) the percent decrement of ^{125}I uptake, and (2) the inhibition of ^{125}I incorporation into iodotyrosines (MIT and DIT), as compared to control values. Lower radioactive T_3 and T_4 concentration in experimental samples than in control samples is also an indicator of antithyroid activity.

C. Inhibition of thyroid hormones deiodination

There are substances that alter the effects of thyroid hormones by inhibiting iodothyronine deiodinases and, thus, conversion of thyroxine (T_4) to its more active metabolite triiodothyronine (T_3). A system using liver microsomes is commonly used.[27-29]

1. Male Sprague-Dawley rat livers are collected, minced, washed in ice-cold buffer (10 m*M* Tris/HCl, pH 7.4) and homogenized for density gradient centrifugation. The microsomal protein fraction is then collected for the assay.
2. Microsomal fractions (100 μg), thyroxine (10 μmol/ℓ), and either blank control, PTU standard, or suspected inhibitor is incubated in 100 m*M* tris buffer (pH 7.4) for 20 min at 37°C. The reaction is stopped and iodothyronines extracted with ethanol at 4°C.
3. After centrifugation the triiodothyronine (T_3) concentration is measured by radioimmunoassay from the ethanolic supernatant.

II. In Vivo Assays

A. Suppression of thyroid gland activities (uptake, organification, hormone release) by acute administration of test material (rats and mice). The suppression of iodide uptake by the thyroid gland after acute administration of test materials in mice, although less sensitive than the in vitro assays, is a rapid, simple, and reproducible in vivo screening procedure[30] (Figure 2).

1. Albino female mice (CD strain) 3 to 4 weeks old, fed on a low iodine diet (Remington) for 15 to 30 days are used in groups of 4 to 5 animals each, for this test.
2. The control blank, methimazole (MMI) as standard, and material to be tested are injected subcutaneously twice at 1-hr intervals. Carrier-free ^{125}I (0.5 μCi) is administered i.p. with the last injection. Three hours later the mice are sacrificed and the thyroids removed for measurement of ^{125}I uptake into the glands.

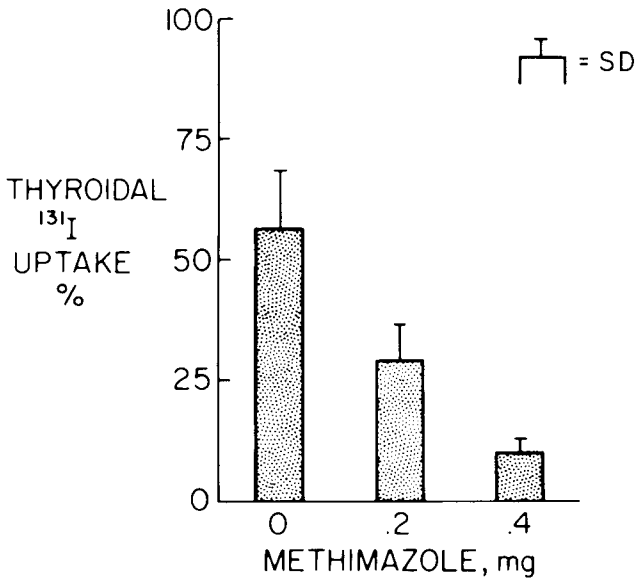

FIGURE 2. In vivo suppression of thyroid radioactive iodine uptake in mice.

B. Goitrogenicity (increase thyroid weight) and antithyroid activity (AA) (suppression of thyroid gland function) by chronic administration of test material, usually, in the rat. Chronic exposure to suspected goitrogens provides a clearer picture of their effects. Not only can the thyroid gland be studied for goitrogenesis and antithyroid effects (AA), but blood samples can also be collected for measurement of thyroid hormones (T_4, T_3, and TSH) and thyroid autoantibodies. In addition, stool and urine samples can be collected for measurement of relevant metabolic products.[19,24,25,31-35]

1. Female rats 60 to 70 g initial weight, are placed in groups (4 to 8 rats each) and fed a low iodine diet (Remington) for 10 days prior to exposure. Control, standard (MMI or PTU), and test materials are administered for at least 30 days in the drinking water or mixed in the diet. The iodine content of the text material should be measured and iodine supplemented if necessary to ensure an equal intake among groups.
2. After the exposure period, rats are injected with 1.0 μCi of ^{125}I and anesthetized 4 hr later. Blood is collected by cardiac puncture and the thyroid glands are removed, weighed, and processed for histology and measurement of AA. Serum is stored at −70°C until radioactivity reaches background levels for measurement of T_3, T_4, and TSH.

C. Other parameters related to goitrogenesis[36,37]

1. Biliary clearance of thyroxine in rats can be determined by injection with radioactive T_4 and biliary cannulation for collection and measurement of T_4 and T_4-glucuronide.[13,14,29,38,39]
2. The peripheral metabolism of thyroxine (T_4) is determined from analysis of liver homogenates.[27-29]
3. The mitochondrial fraction of the homogenates is also collected and measured for mitochondrial 1-α-glycerophosphatedehydrogenase activity, a sensitive indicator of the metabolic action of thyroid hormones in rats.[14,39]

4. Gastrointestinal loss of thyroxine is determined by i.p. injection of radioactive-T_4 in rats fed various diets for 2 to 4 days and the excreta collected and measured for T_4.[40]

D. Induction of lymphocytic or autoimmune thyroiditis (positive circulating antithyroid antibodies, thyroid immunofluorescence, and lymphocytic infiltration) by administration of test material in susceptible animal strains. Autoimmune thyroiditis (AT) occurs spontaneously or can be induced experimentally in a large variety of animals (monkey, dog, chicken, guinea pig, mouse, and rat) providing useful experimental models for the study of the human disease.[7,35,41-45]

1. An appropriate animal model, such as the Buffalo rat[42,43] is injected subcutaneously with a suspected agent for several weeks. At the end of the exposure period, the serum is collected for measurement of thyroid hormones and antithyroglobulin antibodies (TgAb), and the thyroid gland removed, weighed, and processed for histological examination.

General properties, sources, distribution, toxicology, and pharmacokinetics of each class of goitrogenic and/or antithyroid compounds will be discussed separately in the following chapters.

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