RADIATION RESEARCH **174**, 496–516 (2010)
0033-7587/10 $15.00

DOI: 10.1667/RR2243.1

A Physiological Systems Model for Iodine for Use in Radiation Protection

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Leggett, R. W. A Physiological Systems Model for Iodine for Use in Radiation Protection. *Radiat. Res.* 174, 496–516 (2010).

This paper summarizes the biokinetic database for iodine in the human body and proposes a biokinetic model for systemic iodine for use in dose assessments for internally deposited radioiodine. The model consolidates and extends existing physiological systems models describing three subsystems of the iodine cycle in the body: circulating inorganic iodide, thyroidal iodine (trapping and organic binding of iodide and synthesis, storage and secretion of thyroid hormones), and extrathyroidal organic iodine. Thyroidal uptake of inorganic iodide is described as a function of stable iodine intake (Y, μg day^{-1}) and thyroidal secretion of hormonal iodine (S, μg day^{-1}). Baseline parameter values are developed for reference adults with typical iodine intake. Compared with the current systemic biokinetic model of the International Commission on Radiological Protection (ICRP) for occupational intake of radioiodine, the proposed model predicts higher absorbed doses to the thyroid per unit uptake to blood for very short-lived iodine isotopes, similar absorbed doses to thyroid for iodine isotopes with half-life of at least a few hours, and substantially higher estimates of absorbed dose to stomach wall, salivary gland and kidneys for most iodine isotopes. Absorbed dose estimates for intravenous administration of radioiodine-labeled thyroid hormones based on the proposed model differ substantially in some cases from current ICRP values. © 2010 by Radiation Research Society

1. INTRODUCTION

Iodine is an essential component of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3), which regulate metabolic processes and are critical to growth and development (*1–3*). Several tens of micrograms of inorganic iodide are trapped daily by the human thyroid and used for synthesis of T_4 and T_3. Hormonal iodine is largely reduced to inorganic iodide and recycled by the body after use of T_4 and T_3 by tissues, but the body's iodine supply must be supplemented with dietary iodine due to obligatory losses in excreta. A number of physiological systems models have been developed to describe quantitative aspects of the iodine cycle in the human body (*4–14*).

Radioiodine is of concern as an environmental contaminant, but it has a number of beneficial uses in medicine, research and industry. Iodine-131 (half-life, 8.02 days) typically is the main contributor to absorbed dose from internally deposited activity from a few days to several weeks after an incident involving release of fresh fission products to the environment. The shorter-lived isotopes ^{132}I (2.3 h), ^{133}I (20.8 h), ^{134}I (52.5 m), and ^{135}I (6.57 h) may add significantly to absorbed doses in the first few days after release of fresh fission products (*15*) and may be more effective per unit absorbed dose than ^{131}I in producing adverse effects on the thyroid (*16, 17*). Beneficial applications of radioiodine resulting in intended or potentially accidental intakes include the use of ^{131}I in the diagnosis and treatment of thyroid disease and in biological and biochemical research, ^{123}I (13.3 h) and ^{124}I (4.18 days) in positron emission tomography, and ^{125}I (59.4 days) in medicine, biology, agriculture, geology and hydrology.

A three-compartment model developed by Riggs (*5*) for use in physiological and clinical studies has been applied for many years by the International Commission on Radiological Protection (ICRP) as its primary biokinetic model for occupational or environmental intake of radioiodine (Fig. 1) (*18, 19*). The compartments and transfers in the Riggs model represent absorption of dietary iodine to blood as inorganic iodide; competition between thyroidal and renal clearance for circulating inorganic iodide; production, storage and secretion of hormonal iodine by the thyroid; deiodination and recycling of secreted hormonal iodine; and fecal loss of some iodine in hormone metabolites.

Variations of the Riggs model and more detailed biokinetic models for iodine have been developed for special applications in radiation protection, including age-specific dosimetry of internally deposited radioiodine for application to environmental exposures (*20–22*), estimation of absorbed doses to patients from medical applications of radioiodine (*12, 23–27*), absorbed dose to the embryo/fetus or nursing infant from intake of radioiodine by the mother (*28–31*), and reduction of absorbed dose to thyroid from radioiodine by adminis-

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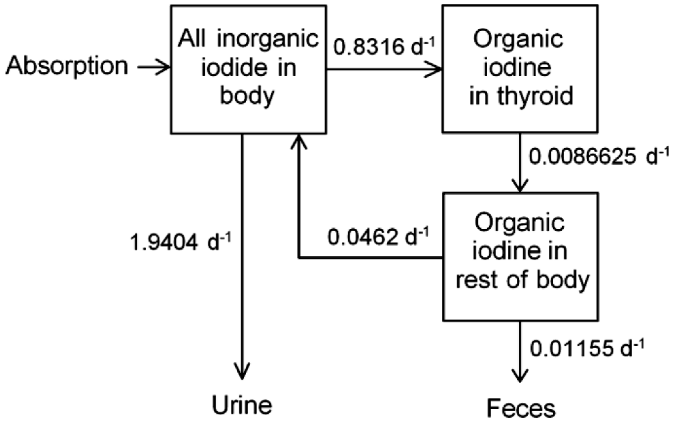

FIG. 1. Biokinetic model for iodine introduced by Riggs (*5*) and widely used in radiation protection, with the ICRP's current parameter values for workers (*18, 19*).

tration of potassium iodide (*32–34*). A model of Berkovski (*28–30*) for the pregnant or nursing mother and a model of Johannsson *et al.* (*27*) designed for applications in nuclear medicine provide additional details of the early biokinetics of inorganic iodide aimed at improving the dosimetry of short-lived radioiodine.

The ICRP is updating its reports on occupational intakes of radionuclides and subsequently will revisit its models and dose coefficients for members of the public. The updated reports continue a trend toward more physiologically realistic and flexible biokinetic models that can be adapted to a variety of problems in radiation protection. In contrast to many of the specialized biokinetic models previously used in ICRP documents, all of the biokinetic models used in the updated reports on occupational intakes of radionuclides are intended as bioassay models as well as dosimetric tools. Also, the structures of the updated models are intended for later extension to different age groups by adjustment of model parameters and to pregnant or nursing women and nursing infants by addition of suitable compartments and associated parameter values.

This paper reviews information on the biokinetics of iodine in adult humans and proposes a physiologically descriptive biokinetic model for systemic iodine that is designed for application to a variety of problems in radiation protection. The model accounts for the influence of dietary stable iodine and the level of thyroid hormone secretion on the biokinetics of iodine and provides a relatively detailed description of the early biokinetics of absorbed iodine aimed at improving radiation dose estimates for short-lived isotopes of iodine. Baseline parameter values are developed for reference workers or adult members of the public with typical iodine intake and thyroid hormone secretion rate.

Section 2 reviews published biokinetic data and models for each of the three main subsystems of the iodine cycle in the human body and assigns baseline exchange rates between the main iodine pools within each of these subsystems on the basis of the review. Section 3 consolidates the quantitative models of the three subsystems developed in Section 2 to form the full biokinetic model for systemic iodine proposed in this paper. Section 4 compares model predictions with observations of radioiodine biokinetics in human subjects. Section 5 compares dose coefficients for intravenous injection, inhalation or ingestion of selected radioisotopes of iodine based on the proposed model with values based on current ICRP models.

2. QUANTITATIVE ASPECTS OF THE IODINE CYCLE IN THE HUMAN BODY

2.1. Dietary intake of stable iodine

The World Health Organization (WHO) recommends daily intake of 150 μg of iodine by adults and 200 μg during pregnancy and lactation to ensure adequate production of thyroid hormones and prevention of goiter and hypothyroidism (*35, 36*). Survey data show large regional variations in dietary iodine, ranging from severely deficient (less than 20 μg day^{-1}) to two orders of magnitude greater than the recommended level (*2, 37–41*). The global median or mean intake by adults is of the order of 150–175 μg day^{-1}. Intake typically is 30–40% lower in women than in men (*42–47*). The following reference values are selected for dietary intake of iodine by adults worldwide: 130 μg day^{-1} for women, 190 μg day^{-1} for men, and 160 μg day^{-1} as a sex-averaged value.

2.2. Absorption of ingested iodine

Iodine occurs in foods mainly as inorganic iodide. Other forms are reduced to iodide in the alimentary tract before absorption (*48, 49*). Absorption is primarily from the small intestine but may occur at other sites along the alimentary tract (*5, 48, 50*). Absorption is rapid and nearly complete in most cases. The absorption rate in fasted subjects was about 5% min^{-1} (*51*). Absorption was slower when iodide was ingested with food but was virtually complete after about 3 h (*51*). More than 99% of iodine administered orally as potassium iodide was absorbed to blood in normal subjects (*52, 53*). In the present model, absorption of iodine from the alimentary tract is assumed to occur only in the small intestine. A baseline absorption fraction of 0.99 is applied.

2.3. Biokinetics of circulating inorganic iodide

Absorbed iodide is distributed rapidly throughout the extracellular fluids (ECF). Most of the iodide that leaves blood returns within an hour (*5, 54, 55*). The iodide ion is largely excluded from most cells but rapidly traverses the red blood cell (RBC) membrane in both directions,

resulting in rapid equilibration between iodide in plasma and RBC water (*5, 56*). For purposes of biokinetic modeling it is reasonable to treat blood iodide as a well-mixed pool (*7*).

Hays and Wegner (*7*) estimated rates of exchange of iodide between blood and extravascular spaces based on computer fits to measurements of activity in tissues and fluids of nine healthy young adult male subjects during the first 3 h after intravenous injection of carrier-free ^{131}I in normal saline. They estimated that iodide leaves blood at a rate of more than 0.4 blood volumes per minute. Equilibrium between blood and a large extracellular space occurred within 10 min. Equilibrium between blood and a more slowly diffusible tissue space was virtually complete within 1 h. Roughly one-fourth of the injected activity was excreted in urine during the first 3 h, and a greater quantity was secreted in saliva and gastric juices and largely recycled to blood during that time. The thyroid accumulated about 13% of the injected amount on average during the first 3 h.

Circulating iodide is concentrated in the salivary glands and stomach wall by active transport (*3*). It is subsequently secreted into the alimentary tract contents in saliva and gastric juice and nearly completely reabsorbed to blood over the next few hours. The concentration of iodide in these secretions typically is 20–40 times its concentration in plasma. As a central estimate the rate of clearance of plasma iodide in saliva plus gastric secretions is about 43 ml/min (range, 36–49 ml/min) (*7, 55, 57, 58*). Harden *et al.* (*58*) estimated that gastric secretion represented about two-thirds of total salivary plus gastric clearance of activity from blood at 40–70 min after intravenous injection of ^{132}I into seven adult male subjects. There is a delay of about 20 min between uptake of iodine by the salivary glands and stomach wall and appearance in the stomach contents and a delay of about 30 min between the peak concentration in plasma and the peak concentration in secretions into the alimentary tract (*5, 7*).

The thyroid and kidneys are in competition for blood iodide and hence for the body's supply of iodide due to the rapid recycling of total-body iodide through blood. Normally more than 90% of the loss of iodine from the body is due to renal clearance of iodide. Little inorganic iodide is lost in feces. Fecal excretion of iodine arises primarily from biliary secretion of organic iodine as T_4 that has been inactivated in the liver (*25*). Sweat does not appear to be an important mode of loss of iodide except perhaps in areas with low dietary iodine, in hot climates, or in athletes or other persons who exercise vigorously and frequently (*54, 59*).

Iodide in blood plasma is filtered by the kidneys at the glomerular filtration rate. About 70% of the filtered iodide is reabsorbed to blood, and the rest enters the urinary bladder contents and is excreted in urine (*60, 61*). Renal clearance expressed as the volume of plasma iodide or blood iodide cleared per unit time is nearly constant over a wide range of plasma concentrations for a given age and sex. As a central estimate, renal clearance is about 37 ml plasma/min for euthyroid adult males (*54, 55, 62*). Renal clearance of iodide expressed as milliliters of plasma per minute appears to be about 25–30% lower on average in women than in men, but fractional loss of total-body iodide in urine per unit time is similar for men and women (*54, 63*).

The concentration of radioiodide in the kidneys may exceed that in most extrathyroidal tissues for a brief period after acute input into blood. In rats the peak concentration in the kidneys occurred about 15 min after intravenous injection (*64, 65*), at which time the kidneys contained a few percent of the injected amount (*64*). In rats and mice, the concentration of radioiodine in the kidneys was similar to that in the salivary glands during the early hours after intravenous or intraperitoneal injection (*65, 66*). Data on laboratory animals generally indicate that the concentration of radioiodide in the kidneys declines rapidly and is not much greater than that in most other organs by a few hours after administration (*67–69*). Using imaging data for ^{124}I (generally derived at 4–44 h after administration as iodide) as a tracer for ^{131}I in patients with thyroid cancer, Kolbert *et al.* (*70*) estimated that the absorbed dose to kidneys from ^{131}I was on average roughly half of the absorbed dose to the salivary glands.

Data on uptake of radioiodide by the liver are variable. Animal data suggest that the liver accumulates a few percent of radioiodide soon after ingestion or intravenous administration but much less per gram of tissue than do the kidneys (*64, 66, 69*).

Typical *transfer coefficients* for inorganic iodide between major pools, as indicated by the information summarized above, are shown in Fig. 2. A *transfer coefficient* is defined as fractional transfer of the contents of the source compartment per unit time. The model in Fig. 2 builds on a model developed by Hays and Wegner (*7*) based on bioassay and external measurements of ^{131}I in young adult males during the first 3 h after intravenous injection. The present model modifies some transfer coefficients in the Hays-Wegner model to reflect central data from collected studies and to account for a difference in the assumed size of the blood iodide pool. A compartment representing iodide in kidneys is included to model the elevated activity in kidneys observed soon after entry of inorganic radioiodide into blood. A compartment representing inorganic iodide in liver is added for completeness, in that the liver is addressed explicitly in the model because it is an important repository for organic iodine rather than inorganic iodide. The transfer coefficients from blood to kidneys and to liver shown in Fig. 2 are consistent with the limited information for laboratory animals and human subjects summarized above.

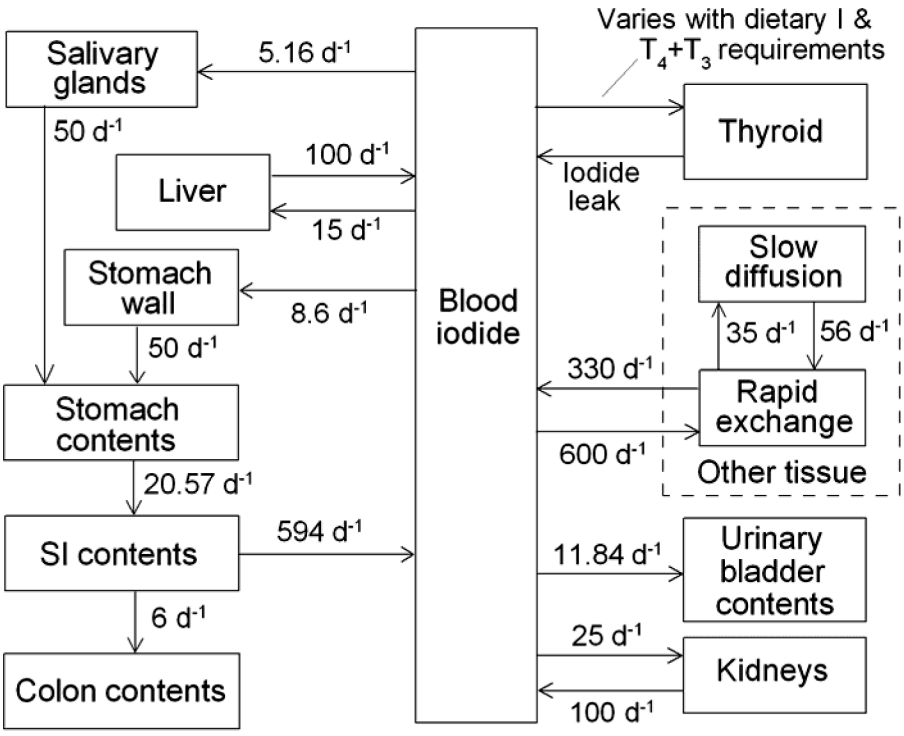

FIG. 2. Estimated rates of exchange of inorganic iodide between major pools. A model of Hays and Wegner (*7*) based on measurements on healthy young adult males was used as a starting point, but data from a number of other studies are reflected.

The following description of the basis for the transfer coefficients shown in Fig. 2 is for a reference adult male (*71*) insofar as anatomical or physiological features are required in the derivations. For reasons discussed in a later section, the derived transfer coefficients are expected to apply equally well to adult females.

Blood iodide represents iodide in blood plasma plus iodine in RBC water and is treated as a well-mixed pool. Transfer coefficients reported in the literature in units of milliliters of plasma per minute are assumed to apply to total blood iodide. For a reference adult male the effective volume of the compartment called Blood iodide is estimated as 4500 ml, based on 3000 ml of plasma and 1500 ml of RBC water. The transfer coefficient describing renal clearance of iodide from blood is based on clearance of 37 ml plasma/min indicated earlier as a central estimate for adult males: (37 ml min^{-1}) $\times$ (1440 min day^{-1})/(4500 ml) = 11.84 day^{-1}. The sum of transfers from Blood iodide to Salivary glands and Stomach wall is based on a central estimate of 43 ml plasma/min for the total rate of secretion of iodide in saliva plus gastric secretions. Division of flow between Salivary glands and Stomach wall is based on reference values (*71*) for daily secretions in saliva (1200 ml) and gastric juice (2000 ml). For example, Stomach wall is assumed to receive 100% $\times$ 2000/(1200 + 2000) = 62.5% of the total flow to these compartments, so that the transfer coefficient from Blood iodide to Stomach wall is 0.625 $\times$ 43 ml min day^{-1} $\times$ 1440 min day^{-1}/(4500 ml) = 8.6 day^{-1}. A transfer coefficient of 50 day^{-1} from Salivary glands or Stomach wall to Stomach contents (Fig. 2) is based on an assumed removal half-time of 20 min in each case. The baseline transfer coefficients describing emptying of the stomach and small intestine (SI) are reference values for total diet from the ICRP's Human Alimentary Tract Model (HATM) (*72*); alternate values may be appropriate in specific cases. The transfer coefficient from SI contents to Blood iodide is derived from the baseline absorption fraction of 0.99. The transfer coefficients associated with Other tissue are essentially the values derived by Hays and Wegner (*7*) by a computer fit to measurements on young adult males. The transfer coefficient from Blood iodide to Other tissue was increased moderately to improve fits to some data sets addressed later. The transfer coefficients associated with the kidneys and liver were set to give a peak radioiodide content in these organs of ~5% and ~3%, respectively, of the administered amount (assuming no decay) at about 15 min after intravenous injection, followed by a relatively fast decline in the concentration in each case (a biological half-time of 10 min).

2.4. Behavior of inorganic iodide and organic iodine in the thyroid

2.4.1. Functional unit of the thyroid

The basic unit of cellular organization within the thyroid is the follicle, a spherical structure that is

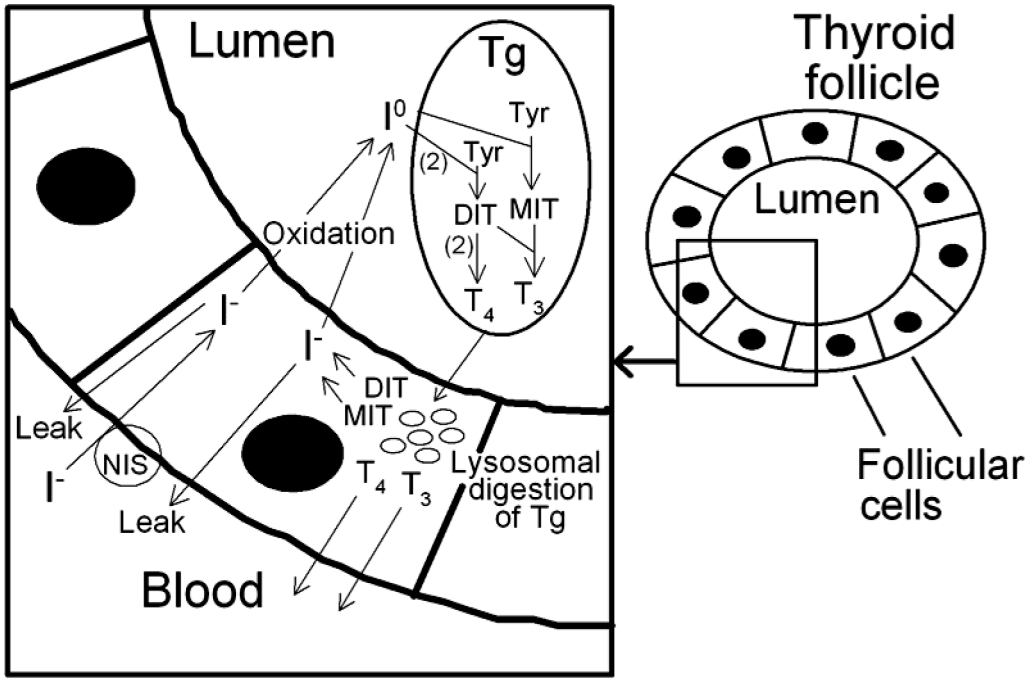

FIG. 3. Diagram of a thyroid follicle showing main steps in synthesis and secretion of T_4 and T_3 (steps described in main text). I^- = iodide, I^0 = neutral iodine, NIS = sodium-iodide symporter, Tg = thyroglobulin, Tyr = tyrosine, MIT = monoiodotyrosine, DIT = diiodotyrosine.

typically a few hundredths of a millimeter in diameter. Each follicle is composed of a single layer of epithelial cells enclosing a lumen filled with a viscous material called colloid (Fig. 3). The colloid consists mainly of thyroglobulin (Tg), a protein synthesized by follicular cells and secreted into the lumen. Thyroglobulin serves as a matrix for production and storage of T_4 and T_3 (*73*).

2.4.2. Regulation of thyroid hormone production and secretion

Production and secretion of T_4 and T_3 are regulated mainly by a feedback mechanism involving thyroid-stimulating hormone (TSH), which is produced and secreted by the pituitary gland. Secretion of TSH is inhibited or accelerated by small increases or decreases, respectively, in plasma T_4 and T_3 concentrations. TSH stimulates uptake (trapping) of plasma iodide passing through the thyroid, conversion of trapped iodide to T_4 and T_3, and release of T_4 and T_3 into the bloodstream (*3*).

The thyroid also has some capacity to autoregulate accumulation and organification of iodide and secretion of hormones in response to changes in availability of iodide. Thyroid autoregulation may involve an iodide concentration-dependent control of production of hydrogen peroxide (H_2O_2), which is generated in follicular cells and required for thyroid hormone synthesis (*73*). Generation of H_2O_2 is limited by a high intracellular concentration of iodide and stimulated by a low intracellular concentration of iodide. Acute intake of a large mass of iodine may result in nearly complete inhibition of H_2O_2 generation and temporary blockade of synthesis of thyroid hormone. There is gradual escape from acute blockade as the iodide concentration in follicular cells becomes too low to maintain the inhibitory effect (*73*). During prolonged intake of high levels of iodine the thyroid gland often is able to escape the blocking effect and resume production of thyroid hormone (*74*).

2.4.3. Thyroidal uptake of iodide and synthesis of hormones

Iodide is actively transported from blood plasma into thyroid follicular cells at the plasma membrane by a protein molecule called the sodium-iodide symporter (NIS), which is also present in substantial quantities in gastric mucosa and salivary glands (*3*). A normal thyroid can concentrate the iodide ion to 20–40 times its concentration in plasma. Some of the iodide entering the thyroid leaks back into blood, but most of it diffuses across the follicular cell and enters the lumen, where it is converted to organic iodine.

Berson and Yalow (*75*) studied the kinetics of thyroidal ''trapping'' (uptake from blood) and ''binding'' (organification) of intravenously injected ^{131}I by the thyroid in 24 hyperthyroid and three euthyroid subjects, first with no inhibition of binding and later with administration of a drug that inhibited binding. The investigators concluded that the rate of binding of trapped iodide is substantially greater than the rate of

return of trapped iodide to blood. When iodide binding was blocked before administration of ^{131}I, activity in the thyroid reached a peak at times varying from several minutes to an hour or more after injection. In ~80% of the cases the rate of loss of trapped ^{131}I from the blocked thyroid was in the range 0.015–0.047 min^{-1} (22–68 day^{-1}).

Robertson *et al.* (*76*) estimated the rate of binding of trapped iodide by the thyroid and the rate of return of trapped iodide to plasma (exit rate) in 15 hyperthyroid and seven euthyroid subjects by kinetic analysis of time-dependent plasma concentrations and thyroid accumulation of intravenously injected ^{131}I. The binding rate was significantly greater in hyperthyroid subjects than in euthyroid subjects, but no significant difference was found in the exit rate in the two groups. The mean exit rate (± standard deviation) for all 22 subjects was 0.025 ± 0.013 min^{-1} (36 ± 19 day^{-1}). The binding rate averaged 0.110 ± 0.042 min^{-1} (160 ± 60 day^{-1}) in the hyperthyroid subjects and 0.066 ± 0.039 min^{-1} (95 ± 56 day^{-1}) in the euthyroid subjects.

After diffusing across the follicular cell, iodide is transported across the luminal membrane into the follicular lumen by a protein called pendrin. Iodide entering the lumen is oxidized at the cell-colloid interface in a reaction requiring H_2O_2 and the enzyme thyroid peroxidase (TPO). The resulting neutral iodine atoms are bound within Tg to specific residues of the amino acid tyrosine (Tyr). Some Tyr residues gain one iodine atom, forming monoiodotyrosine (MIT), and others gain two iodine atoms, forming diiodotyrosine (DIT) (Fig. 4). T_4 and T_3 are formed within Tg in reactions also requiring H_2O_2 and TPO. T_4 is formed by the coupling of two DIT molecules and hence has four iodine atoms. T_3 is formed by coupling of one MIT molecule to one DIT molecule and hence has three iodine atoms (Fig. 4). Iodine comprises 65% and 59% of the mass of T_4 and T_3, respectively. Tg typically contains 10–15 times more T_4 than T_3, but the ratio of T_4 to T_3 varies with the level of iodine in diet. A small amount of reverse T_3 (rT_3), an inactive variant of T_3 with a different configuration of iodine atoms, may also be produced by coupling of MIT and DIT molecules. Typically, less than 40% of the total iodine in Tg is contained in T_4, T_3 and rT_3 and the rest is contained in uncoupled MIT and DIT (*2, 3, 73, 77*).

T_4 is produced only in the thyroid. Approximately 20% of the circulating T_3 normally is produced in the thyroid, and the rest is produced from T_4 in extrathyroidal tissues by removal of an iodine atom from the outer ring of T_4 by the same deiodinating enzyme found in the thyroid (*77, 78*).

The thyroid adapts to prolonged reductions or increases in iodine intake by adjusting its rate of uptake of iodide from blood. Equilibration of thyroidal uptake of iodide to an altered mean iodine intake requires

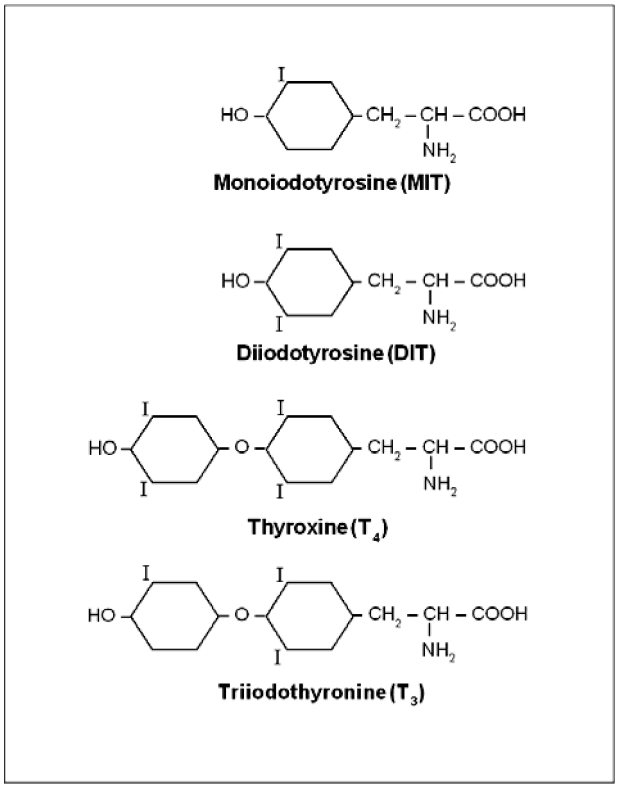

FIG. 4. Structure of the thyroid hormones and precursors [after refs. (*3, 77*)]. The structure of tyrosine is that of MIT minus the iodine atom. The structure of reverse T_3 (rT_3) is that of T_3 with the inner and outer rings reversed; i.e., the outer ring of rT_3 has two iodine atoms and the inner ring has one.

several weeks in adult humans (*79*). For example, if iodine intake is reduced over an extended period, there is a gradual increase in the number of transport molecules (NIS) in the plasma membranes of thyroid follicular cells (*3*) and a gradual increase in thyroid vascularity and mass. If these adjustments are insufficient to replace secreted hormonal iodine, the thyroid eventually decreases its synthesis of T_4 while maintaining a normal level of synthesis of the more active T_3, and there is an increase in fractional conversion of T_4 to T_3 in extrathryoidal tissues (*3, 78, 80*). Because conversion to T_3 normally accounts for only 35–40% of the clearance of T_4 from extrathyroidal tissues (*81*), this homeostatic mechanism can provide a sufficient supply of thyroid hormones to tissues at relatively low levels of dietary intake of iodine. These adaptive mechanisms may allow the thyroid to produce an adequate supply of hormones even if average dietary iodine remains well below recommended intake levels. With severe and prolonged dietary iodine deficiency, however, the supply of thyroid hormones may fall below the level required to maintain normal functions (hypothyroidism) as obligatory losses in excreta deplete the body of iodine. The adverse effects of iodine insufficiency are variable but may include enlargement of the thyroid, reduced metabolic rate, cold intolerance, weight gain and mental

TABLE 1
Relationship of 24-h Uptake of Ingested Radioiodine by Thyroid (U) and Average Daily Urinary Excretion of Stable Iodine (E) in the Same Group of Adult Subjects

Study	No. of subjects[a]	Observed values[b]	
		E (μg day^{-1})	U[c] (%)
Choufoer *et al.* (*82*), New Guinea	30[d]	4.1 ± 0.3	88.5 ± 1.2
Adams *et al.* (*83*), New Guinea	6	5.3 ± 0.7	89.3 ± 4.4
Stanbury *et al.* (*84*), Argentina	6	16.5 (6.2–23.5)	71.6 (68.8–74.5)
	25	23.6	69.1
Ermans *et al.* (*85*), Central Africa	4	27.5 (16.2–47)	82.8 (72–90)
Ingbar and Freinkel (*86*), Massachusetts, U.S.	2	73.9 ± 23.0	39.4 ± 7.0
	3	167 ± 18.5	24.4 ± 2.8
Colard *et al.* (*87*), Belgium	7	78 ± 13	46 (32–52)
DeGroot (*88*), Massachusetts, U.S.	4	128 ± 33	27.1 ± 2.6
Stanbury *et al.* (*84*), Massachusetts, U.S.	2	145 ± 1	29.8 ± 1.8
	1	335	15.2
Ohtaki *et al.* (*89*), Japan	7	175	23.2 (13.2–32.3)
Nagataki *et al.* (*90*), Japan	5	210 (100–379)	19 (14.8–24.3)
Nelson *et al.* (*91*), California, U.S.	132	303 ± 41	17.6 (2–37)
Caplan *et al.* (*92*), Wisconsin, U.S.	44	351 ± 6.8	12.1 ± 0.9
	7	385 ± 60	9.6 ± 0.7
	2	966 ± 160	5.7 ± 1.4
Hooper *et al.* (*93*), New Mexico, U.S.	20	410 ± 55	11.2 ± 1.2
Pittman *et al.* (*94*), Alabama, U.S.	53	680 ± 13	15.4 ± 1.1
Nagataki *et al.* (*90*), Japan	4	1132 (878–1690)	12.5 (10.2–15.8)
Ohtaki *et al.* (*89*), Japan	7	1523 ± 356	16.7 (9.5–26.6)
Nagataki *et al.* (*90*), Japan	2	15,540 (13,780–17,300)	5.1 (2.6–7.5)

[a] Refers to subjects in which U was determined; E was sometimes determined in a subgroup.
[b] Mean and standard error or range when available.
[c] Observed values for radioiodine corrected for radioactive decay.
[d] Includes 12 teenagers (ages 13–18 years).

sluggishness, which in severe cases can result in psychoses and if uncorrected in institutionalization.

Adaptation of thyroidal clearance of iodide to dietary intake results in an inverse relationship between U and E, where U is fractional uptake of ingested radioiodine by the thyroid at 24 h and E (μg day^{-1}) is the rate of urinary excretion of stable iodine (Table 1). The value U also depends on the rate S (μg day^{-1}) of hormonal iodine secretion by the thyroid. Stanbury *et al.* (*84*) derived the formula $U = S/(S + E)$, based on the assumption that daily accumulation of organic iodine by the thyroid is in mass balance with daily secretion S of hormonal iodine. They derived a central estimate for S of 57 μg day^{-1} from measurements of E and U in a relatively large study group, primarily young adult females, with generally low rates of urinary excretion of stable iodine and high incidence of goiter. The formula $U = 57/(57 + E)$ is still widely used to estimate thyroidal uptake of radioiodine on the basis of urinary iodide. This formula is reasonably consistent with data for populations with iodine intake up to a few hundred micrograms per day (*95*).

Zvonova (*96*) compiled regional data on dietary intake or urinary excretion of stable iodine, thyroidal uptake of radioiodine, and mass of the thyroid in adult humans. Data were collected for populations in Argentina, West Germany, Russia, Denmark, Scotland, Hungary, West New Guinea and seven regions in the U.S. Estimated dietary intake of stable iodine ranged from 5–10 μg day^{-1} in West New Guinea to 250–700 μg day^{-1} in some regions of the U.S. The mean fractional uptake U of ingested radioiodine by the thyroid at 24 h was estimated as 0.14–0.15 for populations with stable iodine intake greater than 400 μg day^{-1}, 0.16–0.27 for intake of 250–330 μg day^{-1}, 0.41–0.45 for intake of 80–85 μg day^{-1}, 0.54–0.59 for intake of 40–54 μg day^{-1}, and about 0.9 for intake of 5–10 μg day^{-1}. The mean thyroid mass varied inversely with stable iodine intake Y. Zvonova derived the relationship $U = 85/(85 + Y)$ based on an assumed balance of thyroidal production and secretion of hormones. The value S = 85 μg day^{-1} was derived by fitting the collected data for Y and U.

The formulas for thyroidal uptake of radioiodine derived by Stanbury *et al.* (*84*) and Zvonova (*96*) both provide reasonable approximations to reported radioiodine uptake in populations with stable iodine intake up to a few hundred micrograms per day but underestimate uptake in populations on an iodine-rich diet. The underestimates presumably arise because the assumption of balance of thyroidal uptake and hormonal secretion of iodine involves large errors at high levels of dietary stable iodine. Although the rate of accumulation of organic iodine by the thyroid and the rate of loss of iodine from the thyroid both appear to increase at high levels of iodine intake, the mass of iodine secreted as

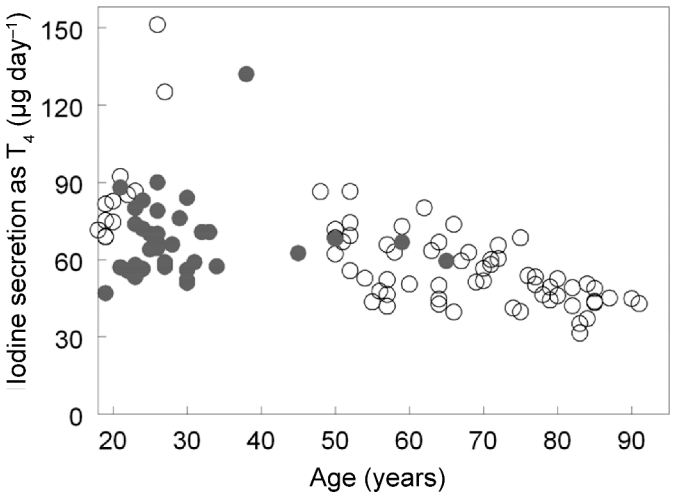

FIG. 5. Rate of secretion of hormonal iodine as T_4 in adult male humans. Data from refs. (*107*) (open circles) and (*43, 53, 111, 115, 116*) (shaded circles).

thyroid hormones appears to remain unchanged (*53, 79, 89, 90, 97, 98*).

2.4.4. Storage and secretion of thyroid hormones

Iodinated Tg is stored within the lumen of thyroid follicles. In adults on an iodine-sufficient diet the thyroid typically stores 5–15 mg of hormonal iodine (*5, 99–103*).

In response to demand for thyroid hormone secretion, iodinated Tg is internalized by follicular cells by pinocytosis and digested in lysosomes. Freed T_4 and T_3 are released to blood, and freed MIT and DIT are deiodinated within the follicular cells by an enzyme called iodotyrosine deiodinase. The iodide released from MIT and DIT presumably exchanges to some extent with the pool of iodide that has been transported from blood into the follicular cell by NIS, but dual-isotope studies on human subjects indicate that these two sources of iodide in follicular cells do not form a well-mixed pool (*104*). Part of the iodide released from MIT and DIT is transferred back to the follicular lumen for further hormone synthesis, and part of it leaks into blood (*3, 73, 104, 105*). The fraction of iodide leaked into blood is variable, resulting in daily fluctuations in the total mass of iodine released by the thyroid to blood despite the nearly constant rate of release of hormonal iodine (*104*). The leak may be small compared with released hormonal iodine for moderate to low dietary intake of iodine but large for high intake.

The estimated rate S of secretion of hormonal iodine by the thyroid in individual euthyroid adult humans ranges from less than 30 to more than 150 μg day^{-1} (*5, 53, 79, 84, 86, 96, 106–108*). Reference values for S in adults given in reviews and textbooks generally are in the range 55–85 μg day^{-1} (*5, 10, 11, 77, 79, 96, 109, 110*). As illustrated in Fig. 5, thyroid hormone secretion declines with increasing adult age, at least after the fifth or sixth decade (*53, 107, 111–114*). The secretion rate is about one-third lower on average in women than in men, although there is some overlap in individual measurements for women and men (*53, 86, 111*). The following reference values of S for adults through age 65 years (hence applicable to workers) are based on collected data on thyroidal secretion of iodine as T_4 at ages 18–65 years and the assumption that T_4 represents 90% of total secretion of hormonal iodine: 52 μg day^{-1} for females, 76 μg day^{-1} for males, and 64 μg day^{-1} as a sex-averaged value.

There appears to be some early secretion of newly formed T_4 and T_3, but this represents less than 5% of the organified tracer (*8, 11*). Most of the iodinated Tg is retained in the follicular lumen for weeks or months. For practical applications it generally suffices to treat iodinated Tg in the thyroid as a well-mixed pool.

Fractional transfer of iodine from thyroid stores to blood per unit time and the corresponding biological half-time of organic iodine in the thyroid depend on the size of current stores, the rate of thyroidal secretion of hormonal iodine (S, μg day^{-1}), and the extent of leakage of iodide from MIT and DIT deiodinated in follicular cells. For example, assuming first-order kinetics and no leakage of iodide from MIT and DIT, the calculated single-passage biological half-time is 54 days based on thyroidal stores of 5 mg of iodine and S = 64 μg day^{-1}, 91 days based on stores of 10 mg and S = 76 μg day^{-1}, and 130 days based on stores of 15 mg and S = 80 μg day^{-1}. The apparent (externally measured) half-time is longer than the single-passage half-time due to recycling of secreted iodine back to the thyroid. The difference in the single-passage and apparent half-time for a given subject depends on the period of observation after acute intake of radioiodine and the level of thyroidal uptake of blood iodide. Reported apparent half-times in adults vary from about 3 weeks to about 1 year and average about 85 days (*20, 22, 117–119*). Most reported apparent half-times have been based on short-term (typically, 2 week) external measurements of ^{131}I disappearance from the thyroid (*20, 22*). Long-term measurements (up to ~5 months) on five workers acutely exposed to ^{125}I vapor indicated a mean apparent half-time of about 130 days (range, 106–186 days) (*119*).

A rounded single-passage biological half-time of 90 days is consistent with central estimates of thyroidal iodine stores and hormonal secretion of iodine, e.g., stores of 10 mg and S = 76 μg day^{-1} in an adult male, and is adopted here as a baseline value. The corresponding apparent half-time calculated from the proposed model with baseline parameter values is about 120 days, assuming a 5-month observation period starting at the time of peak activity in the thyroid.

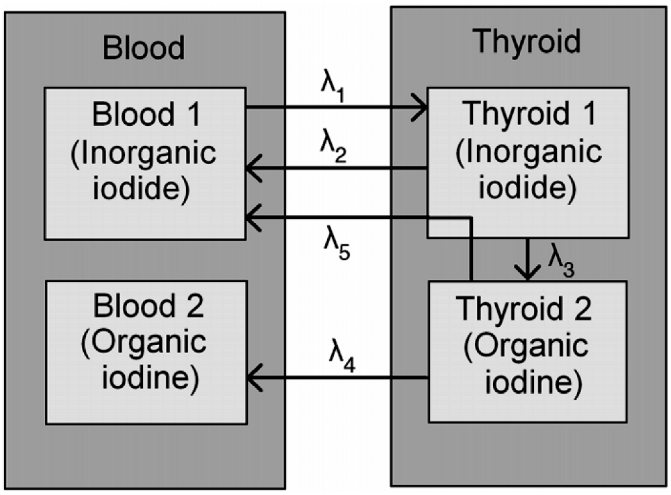

FIG. 6. Schematic of the movement of iodine between blood and the thyroid and within the thyroid. Baseline values of the transfer coefficients determined for adults are $\lambda_1 = 7.26$ day^{-1}, $\lambda_2 = 36$ day^{-1}, $\lambda_3 = 95$ day^{-1}, $\lambda_4 = 0.0077$ day^{-1}, and $\lambda_5 = 0$ day^{-1}.

2.4.5. Summary: Typical biokinetics of thyroidal iodine in adults

A schematic of the net movement of inorganic iodide and organic iodine within the thyroid and between blood and the thyroid is shown in Fig. 6. The schematic reduces the earlier diagram of the steps in synthesis, storage and secretion of thyroid hormones (Fig. 3) to a first-order model. Blood and thyroid are each divided into compartments representing inorganic iodide (Blood 1 and Thyroid 1, respectively) and organic iodine (Blood 2 and Thyroid 2, respectively).

As depicted in Fig. 6, inorganic iodide is transferred from Blood 1 to Thyroid 1 at a rate λ_1 (volumes of the source compartment transferred per day) that depends on dietary intake Y of stable iodine (μg day^{-1}) and thyroidal secretion S of hormonal iodine (μg day^{-1}) as described later. Thyroid 1 leaks iodide back to Blood 1 at the rate λ_2 and transfers iodide to Thyroid 2 at the rate λ_3. The rates λ_2 and λ_3 are set at 36 day^{-1} and 95 day^{-1}, respectively, based on measurements by Robertson *et al.* (*76*) discussed earlier. Thyroid 2 converts inorganic iodide to organic iodine instantaneously, transfers organic iodine to Blood 2 at the rate λ_4 and, as a by-product of the transfer, leaks inorganic iodide into Blood 1 at the rate λ_5. The rate λ_4 is assigned the baseline value 0.0077 day^{-1} corresponding to a biological half-time of 90 days. The leak of inorganic iodide from Thyroid 2 to Blood 1 represents the net result of transfer of iodinated Tg from the thyroid follicular lumen into the follicular cell, digestion of Tg in lysosomes, transfer of released T_4 and T_3 to blood, deiodination of released MIT and DIT in the follicular cell, recycling of most of the freed iodide to the follicular lumen, and leakage of the rest to blood. The transfer coefficient λ_5 is assumed to be nonzero only for an iodine-rich diet, as described later.

For dietary stable iodine up to a few hundred micrograms per day (the precise value depends on S) it is assumed that $\lambda_5 = 0$ (i.e., all iodide released in follicular cells from deiodination of MIT and DIT is reused to produce thyroid hormones) and that thyroidal uptake of iodide is in mass balance with hormonal secretion of iodine. Under these assumptions plus the assumption that intake and excretion of stable iodine are in balance, the transfer coefficient λ_1 from Blood 1 to Thyroid 1 can be expressed as a function of dietary stable iodine (Y) and thyroidal secretion of hormonal iodine (S). Based on the transfer coefficients from Thyroid 1 to Blood 1 (36 day^{-1}) and Thyroid 1 to Thyroid 2 (95 day^{-1}), the mass of iodide transferred from Blood 1 to Thyroid 1 each day must equal $S \times (36+95)/95$ μg $= 1.38S$ μg to achieve transfer of S μg day^{-1} to Thyroid 2. This means that $\lambda_1 = (1.38S/X)$ day^{-1}, where X (μg) is the mass of iodide in Blood 1 at equilibrium. Daily loss of iodide in urine is 11.84X (μg), where 11.84 (day^{-1}) is the transfer coefficient from Blood 1 to Urinary bladder contents (Fig. 2). Daily loss of iodide in urine is also equal to daily intake Y minus daily fecal excretion. Daily fecal excretion of iodine is approximately $0.02Y + 0.2S$, where 0.02Y is the approximate fecal excretion of inorganic iodide resulting from incomplete absorption of the initially ingested amount (1% loss) and incomplete reabsorption of secreted iodide (an additional ~1% loss), and (as described in a later section) 0.2S represents daily fecal excretion of hormonal iodine. Therefore, $11.84X = Y - 0.02Y - 0.2S$, or $X = (0.98Y - 0.2S)/11.84$. It follows that

$$\lambda_1 = 1.38S/X = 1.38S/[(0.98Y - 0.2S)/11.84] \text{ day}^{-1},$$

$$\lambda_1 = 16.34S/(0.98Y - 0.2S), \quad (1)$$

$$\lambda_1 = 16.34/[0.98(Y/S) - 0.2] \text{ day}^{-1}. \quad (2)$$

Thus λ_1 is determined by the quotient Y/S. The value of Y/S based on gender-averaged reference values for ages 20–65 years (representing workers) is 160 μg day^{-1}/64 μg day^{-1} = 2.5. The same value is derived from reference values for either sex: Y/S = 190 μg day^{-1}/76 μg day^{-1} (males) = 130 μg day^{-1}/52 μg day^{-1} (females) = 2.5. The corresponding transfer coefficient based on Eq. (2) is $\lambda_1 = 16.34/[(0.98 \times 2.5) - 0.2]$ day^{-1} = 7.26 day^{-1}, which is adopted as the baseline value for λ_1. Equation (1) can also be rewritten as

$$\lambda_1 = 16.34S/E, \quad (3)$$

where E is the rate (μg day^{-1}) of urinary excretion of stable iodine.

Equations (1–3) are applicable to any combination of Y and S that gives a transfer coefficient of at least 2.5 day^{-1}. For lower derived values, the transfer coefficient λ_1 from Blood 1 to Thyroid 1 is set at 2.5 day^{-1}, which gives a 24-h thyroid content of about 12% of the ingested amount. This appears to be a reasonable average value for dietary stable iodine in the range 400–2000 μg day^{-1} (*89, 90, 92–94*) but may overestimate average uptake in populations with dietary stable iodine substantially greater than 2000 μg day^{-1}.

The 90-day biological half-time for iodine in Thyroid 2 is applied to all levels of dietary iodine, but for high intake the outflow from Thyroid 2 is divided between Blood 2 and Blood 1 because the leak of iodide from Thyroid 2 to Blood 1 is assumed to be nonzero in this case. The mass of iodine removed daily from Thyroid 2 in excess of hormonal iodine secretion is assumed to be inorganic iodide and is assigned to Blood 1. This is accomplished mathematically by reducing λ_4 to give a transfer to Blood 2 of S μg day^{-1} and assigning a nonzero transfer coefficient λ_5 from Thyroid 2 to Blood 1 that accounts for the difference in total outflow from Thyroid 2. The transfer coefficient from Thyroid 2 to Blood 2 becomes S/C, where C (μg) is the mass of iodine in Thyroid 2. The transfer coefficient λ_5 from Thyroid 2 to Blood 1 becomes $(0.0077 - S/C)$ day^{-1}.

In the proposed model, thyroid blocking is viewed as interference with organification of iodide by the thyroid and represented mathematically as a reduction of the transfer coefficient λ_3 from Thyroid 1 to Thyroid 2. For complete blocking, $\lambda_3 = 0$.

2.5. Behavior of extrathyroidal T_4 and T_3

2.5.1. T_4 as a precursor of T_3 and rT_3

T_3 exerts most of the effects of the thyroid hormones in the body. T_4 has little intrinsic biological activity and serves mainly as a long-lived precursor to the more active and shorter-lived T_3. T_4 can be converted to T_3 outside the thyroid when increased thyroid hormone activity is required or to inactive rT_3 when excess thyroid activity is present. Much of the extrathyroidal conversion of T_4 to T_3 occurs in the liver and kidneys. Approximately 80% of T_4 secreted by the thyroid is metabolized by conversion to either T_3 (typically 35–40%) or rT_3 (40–45%) (*78, 81*).

2.5.2. Summary of the biokinetic database

Upon secretion by the thyroid into blood, T_4 and T_3 are rapidly and almost completely bound to plasma proteins. Little if any enters the RBC. Reported concentrations of protein-bound iodine in blood plasma of euthyroid subjects generally are in the range 3–8 μg/100 ml and cluster about 5–6 μg/100 ml (*9, 120–124*).

A number of investigators have studied the kinetics of radiolabeled T_4 after intravenous injection into human subjects (*5, 9, 86, 107, 121, 125–131*). Blood clearance kinetics follows a multi-exponential function with half-times ranging from about 1 h to about 1 week. Rapid early disappearance from plasma may represent mainly distribution throughout the extracellular fluids plus uptake by hepatocytes. A slower decline at later times may represent uptake by cells and binding to intracellular proteins throughout the body, reduction to inorganic iodide due to use of the hormones by cells, and biliary secretion followed by fecal excretion of part of the organic iodine entering the liver. External measurements together with liver biopsy data indicate that the liver accumulates roughly 35% (22–52%) of injected T_4 during the first 3–4 h after administration and contains roughly 25% (14–40%) of extrathyroidal T_4 at equilibrium (*9, 121, 128, 131*).

The kinetics of labeled T_3 has been difficult to determine with much precision, in large part due to interference of iodoproteins generated by metabolism of the injected tracer material (*124, 131*). Human studies indicate high initial uptake of labeled T_3 by the liver but a shorter hepatic retention time than that of T_4 (*132*). The liver content at equilibrium has been estimated as 5–21% of the total extrathyroidal T_3 pool (*25, 132*).

A portion of T_4 or T_3 entering the liver is secreted into the small intestine in bile (*77*). The secreted form is poorly absorbed to blood and is largely excreted in feces (*25*). This accounts for about one-fifth of the loss of organic iodine from extrathyroidal tissues, and reduction to iodide and return to the blood iodide pool accounts for the rest (*82, 86, 106, 122, 130, 133, 134*). Endogenous fecal excretion of organic iodine can become a major source of loss of iodine during periods of low intake of iodine (*82, 135, 136*).

Animal studies indicate that the concentration of organic iodine in the kidneys is at least as high as that in the liver. For example, in rats receiving daily injections of $Na^{125}I$ over a 3-week period, the concentration of labeled T_4 in kidneys was similar to that in the liver, about seven times that in muscle, and more than twice that in heart (*137*). The concentration of labeled T_3 in kidneys was nearly twice that in the liver, eight to nine times that in muscle, and four times that in heart.

Most estimates of the mass of extrathyroidal organic iodine at equilibrium are in the range 500–1000 μg. Most estimates of the biological half-life of T_4 in normal subjects are in the range 5–9 days (*9, 26, 86, 107, 121, 125, 129–131, 134*). The half-life of T_3 is about 1 day (*3, 122, 124, 130, 131, 138, 139*) and that of reverse T_3 (rT_3) is a few hours (*130*). Measurements on 73 euthyroid males of ages 18–91 years indicate that the rate of T_4 production as well as its turnover rate, representing the combined rate of deiodination and fecal excretion,

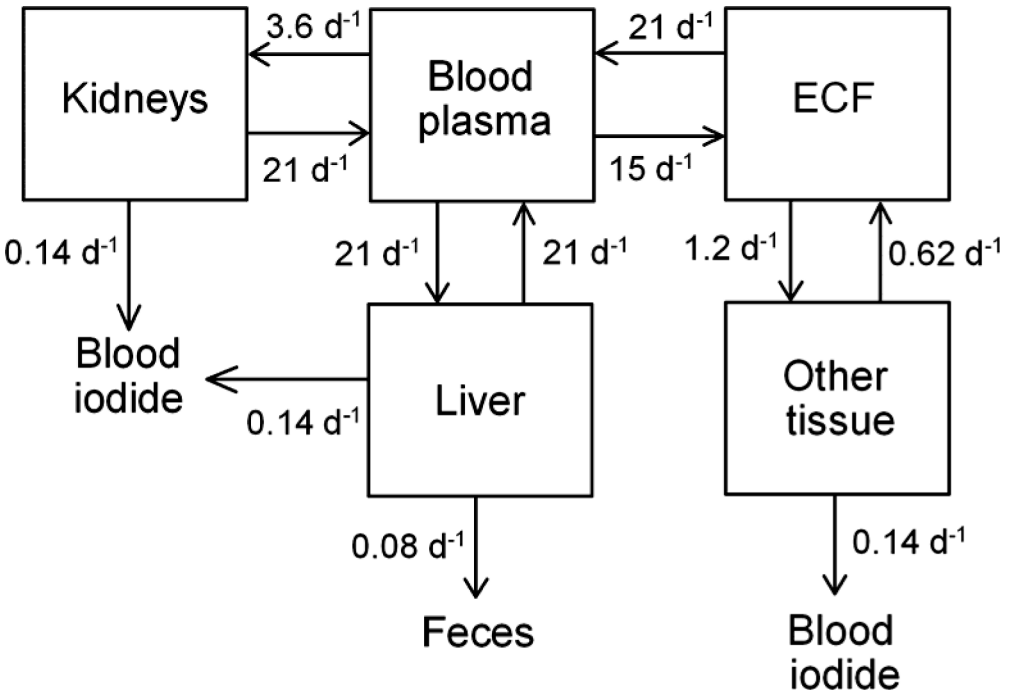

FIG. 7. A model of transfer of extrathyroidal T_4 between major pools, modified from Nicoloff and Dowling (*9*). ECF = extracellular fluid.

decrease with age starting some time before age 50 years (*107*). The half-life of labeled T_4 was estimated as 6.6 days in young adult males and 8–9 days after the fifth decade of life (*107*). In 165 healthy subjects in the age range 18–86 years, measured rates of deiodination of T_4 were similar in male and female subjects in the same age groups (*134*). The half-time of deiodination of T_4 increased with age from about 8 days in the third decade of life to about 13 days in the sixth decade (*134*).

The typical biokinetics of organic iodine in extrathyroidal tissues, as estimated primarily from measurements of labeled T_4, is summarized as a compartment model in Fig. 7. This is a modification of a model developed by Nicoloff and Dowling (*9*) from bioassay and external measurements of ^{131}I after intravenous injection of ^{131}I-labeled T_4 into 13 healthy adult human subjects. The present model adds a compartment representing kidneys and assumed to have the same rate of exchange with blood plasma per gram of tissue as does the liver. Transfer coefficients reported by Nicoloff and Dowling for one of their most extensively studied subjects were modified so that the model yields the following typical values suggested by data from collected studies: the removal half-time of thyroid hormone from the system (i.e., from extrathyroidal tissues and fluids) is 7 days; fecal excretion represents 20% of the loss of thyroid hormones from the system, and return of inorganic iodide to the blood iodide pool represents the other 80%; and the liver and blood plasma each contain one quarter of the extrathyroidal hormones at equilibrium. The following changes in the transfer coefficients of Nicoloff and Dowling were required to reproduce those values: transfer from Liver to Blood plasma was changed from 22 to 21 day^{-1}; transfer from Liver to Feces was changed from 0.14 to 0.08 day^{-1}; and transfer from Blood plasma to ECF was reduced from 19 to 15 day^{-1} to maintain approximately the same total outflow rate from plasma after the addition of Kidneys. The transfer coefficient from Other tissue to Blood iodide (0.14 day^{-1}) was assumed to apply also to transfer from Liver or Kidneys to Blood iodide.

The transfer coefficients in Fig. 7 are used in the full biokinetic model for iodine (described in the next section) as transfer coefficients for extrathyroidal organic iodine. The same rates may be applied in the dosimetry of radiolabeled T_4 because the rates are based mainly on T_4 studies. These rates do not apply to radiolabeled T_3 or rT_3, both of which have substantially faster exchange rates and shorter half-lives than T_4. Transfer coefficients for T_3 and rT_3 intended for dosimetry of radiolabeled T_3 or rT_3 are listed in Table 2. Transfer coefficients for T_3 were derived by adjusting the values for T_4 to achieve reasonable agreement with the more limited biokinetic database for T_3 summarized above. This was achieved by essentially doubling the relatively fast transfer coefficients for T_4 (those between Blood plasma and ECF, Liver or Kidneys), increasing slower transfers other than ECF to Other tissue by roughly a factor of five, and increasing the transfer from ECF to cells (Other tissue) by about a factor of 40. Transfer coefficients for rT_3 were derived by modifying

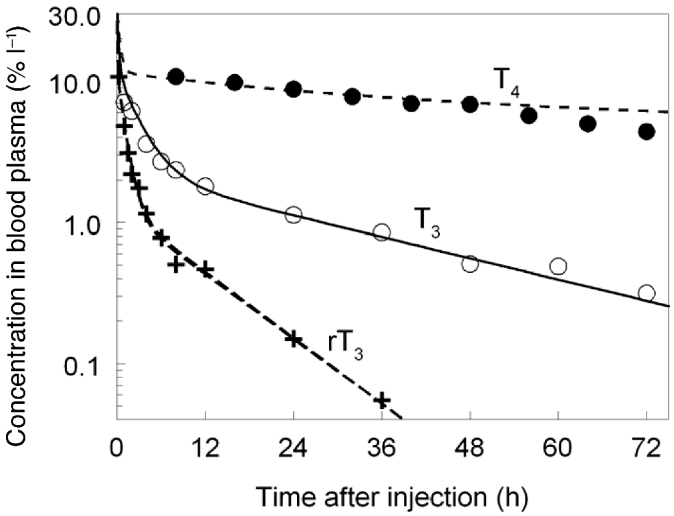

FIG. 8. Plasma disappearance curves generated from the derived transfer coefficients for T_4, T_3 and rT_3 (see Fig. 7 and Table 2) compared with mean observations (*130*) for 10 healthy adult subjects after intravenous injection with radiolabeled T_4, T_3 or rT_3.

TABLE 2
Baseline Parameter Values for Iodine Entering Blood Plasma as T_4, T_3 or rT_3[a]

Pathway	Transfer coefficient (day^{-1})		
	T_4	T_3	rT_3
Plasma to ECF	15	30	90
ECF to Plasma	21	40	120
ECF to Other tissue	1.2	50	150
Other tissue to ECF	0.62	3.0	4.5
Other tissue to Blood iodide	0.14	0.75	2.2
Plasma to Kidneys	3.6	7.0	21
Kidneys to Plasma	21	40	120
Kidneys to Blood iodide	0.14	0.75	2.2
Plasma to Liver	21	40	120
Liver to Plasma	21	40	120
Liver to Blood iodide	0.14	0.75	2.2
Liver to Feces[b]	0.08	0.5	1.5

[a] Transfer coefficients shown for T_4 are the same as the values for all extrathyroidal organic iodine shown in Fig. 7.
[b] Represented as a feed from the liver to small intestine to right colon with negligible residence time in the small intestine.

(increasing) transfer coefficients for T_3 to achieve reasonable agreement of model predictions of plasma disappearance of rT_3 with reported data for rT_3. This was achieved by tripling the rates for T_3 except for Other tissue to ECF, for which the value for T_3 was increased by 50%. Plasma disappearance curves generated by the models for T_4, T_3 and rT_3 are compared in Fig. 8 with the data of Chopra (*130*) for 10 healthy subjects (six men and four women, ages 19–41 years) receiving radiolabeled T_4, T_3, or rT_3 by intravenous injection.

3. PROPOSED IODINE MODEL

3.1. Model structure and baseline parameter values

The proposed biokinetic model for iodine is formed by consolidating the model of circulating inorganic iodide shown in Fig. 2, the model of thyroidal iodine shown in Fig. 6, and the model of extrathyroidal organic iodine shown in Fig. 7. The structure of the full model is shown in Fig. 9. Baseline transfer coefficients for a reference adult are listed in Table 3; these values apply

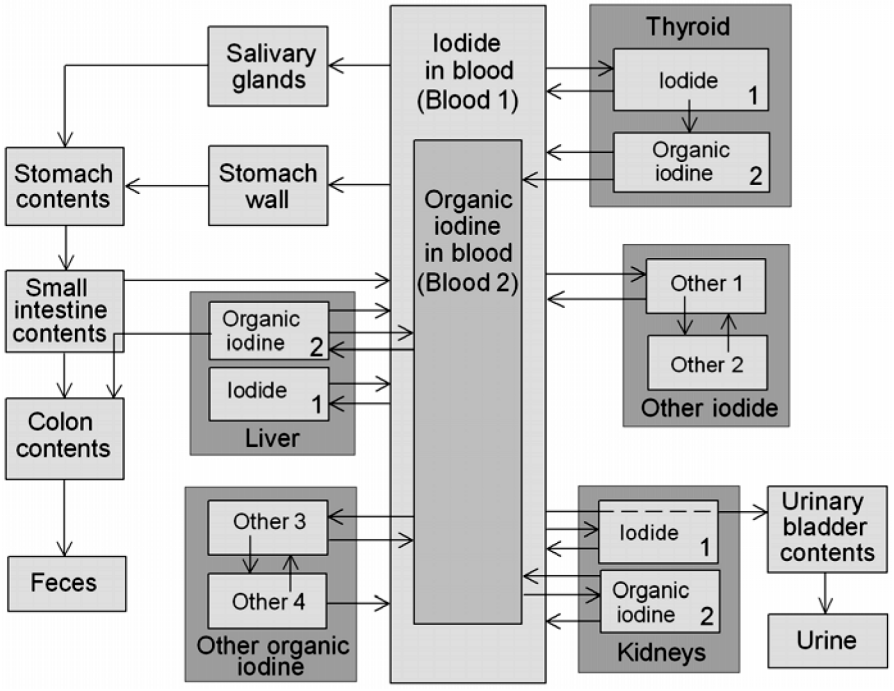

FIG. 9. Structure of the proposed biokinetic model.

TABLE 3
Baseline Parameter Values for the Proposed Biokinetic Model for Systemic Iodine, Applicable to a Reference Adult

Pathway	Transfer coefficient (day^{-1})
Blood 1 to Thyroid 1	7.26[a]
Blood 1 to Urinary bladder contents	11.84
Blood 1 to Salivary glands	5.16
Blood 1 to Stomach wall	8.60
Blood 1 to Other 1	600
Blood 1 to Kidneys 1	25
Blood 1 to Liver 1	15
Salivary glands to Stomach contents	50
Stomach wall to Stomach contents	50
Thyroid 1 to Thyroid 2	95
Thyroid 1 to Blood 1	36
Thyroid 2 to Blood 2[b]	0.0077
Thyroid 2 to Blood 1	0[c]
Other 1 to Blood 1	330
Other 1 to Other 2	35
Other 2 to Other 1	56
Kidneys 1 to Blood 1	100
Liver 1 to Blood 1	100
Blood 2 to Other 3	15
Other 3 to Blood 2	21
Other 3 to Other 4	1.2
Other 4 to Other 3	0.62
Other 4 to Blood 1	0.14
Blood 2 to Kidneys 2	3.6
Kidneys 2 to Blood 2	21
Kidneys 2 to Blood 1	0.14
Blood 2 to Liver 2	21
Liver 2 to Blood 2	21
Liver 2 to Blood 1	0.14
Liver 2 to Right colon contents	0.08
Stomach contents to SI contents	20.57
SI contents to Colon contents	6.0
SI contents to Blood 1	594
Urinary bladder contents to Urine	12

[a] Depends on the ratio Y/S, where Y (μg day^{-1}) is dietary intake of stable iodine and S (μg day^{-1}) is the rate of secretion of hormonal stable iodine by the thyroid.
[b] For high intake of stable iodine the outflow from Thyroid 2 is split between Blood 2 and Blood 1 as described in the text.
[c] Non-zero only for high dietary stable iodine. See text.

to both men and women. The inorganic iodide compartments Other 1 and Other 2 in Fig. 9 are the compartments in Fig. 2 labeled Rapid exchange and Slow diffusion. The organic iodine compartments Other 3 and Other 4 in Fig. 9 are the compartments in Fig. 7 labeled ECF and Other tissue. Blood 1 in Fig. 9 is the compartment in Fig. 2 labeled Blood iodide. Blood 2 in Fig. 9 is the compartment in Fig. 7 labeled Blood plasma.

3.2. Applicability of a common set of parameter values to men and women

Although some quantities used in the derivations of transfer coefficients described earlier are sex dependent, differences in these quantities between average adult males and average adult females tend to offset one another in the calculation of fractional transfers per unit time between compartments. For example, the volume of blood in an adult female typically is about three-fourths of that in a male of the same age, based on reference volumes for blood plasma and RBC given in ICRP Publication 89 (*71*). On average, renal clearance of iodide, expressed in units of ml blood min^{-1}, in adult females also appears to be roughly three-fourths of that in adult males. Thus the derived transfer coefficient from Blood 1 to Urinary bladder contents for an adult female should be similar to that for an adult male because the rate is calculated as blood volumes of iodide cleared in urine each day divided by the blood iodide volume.

More nearly direct determinations of biokinetic quantities for iodine generally do not reveal significant differences with sex in transfer coefficients. For example, an analysis of data for 1420 euthyroid subjects observed by 32 groups of investigators indicated that thyroidal clearance of plasma iodide was independent of the sex and age of the subjects (*140*). Also, sex differences in the rate of deiodination of radioiodine-labeled T_4 were not evident in a study involving large numbers of men and women (*134*). A study used in this paper as the primary basis of transfer coefficients for extrathyroidal organic iodine compartments involved both male and female subjects (*9*), and sex differences are not apparent in the turnover kinetics reported for that study.

The transfer coefficient from Blood 1 to Thyroid 1 is determined by the ratio Y/S, where Y is dietary stable iodine (μg day^{-1}) and S is the rate of thyroidal secretion of stable iodine (μg day^{-1}). Both Y and S are related to energy requirements, and both are estimated to be about one-third lower on average for adult females than adult males. Thus the ratio Y/S and hence the transfer coefficient from Blood 1 to Thyroid 1 derived for adult males should apply reasonably well to adult females.

4. MODEL PREDICTIONS

Model predictions of the distribution of radioiodine in the first few hours after intravenous injection into adult humans, using the baseline transfer coefficients (Table 3), are compared with observations in Figs. 10–13. The open circles in all four figures represent means for nine healthy young adult males (*55*); variability of measurements was reported as mean coefficients of variation, which were approximately 12%, 78%, 19% and 23% for blood plasma, salivary plus gastric secretions, urine and thyroid, respectively. The close agreement in Figs. 10–12 between predictions and observations represented by open circles is to be expected because the transfer coefficients dominating model predictions in these cases were based in part on these observations. The triangles in Fig. 10 represent median values determined from data plots for 5–13 individual euthyroid patients (*62*); individual measure-

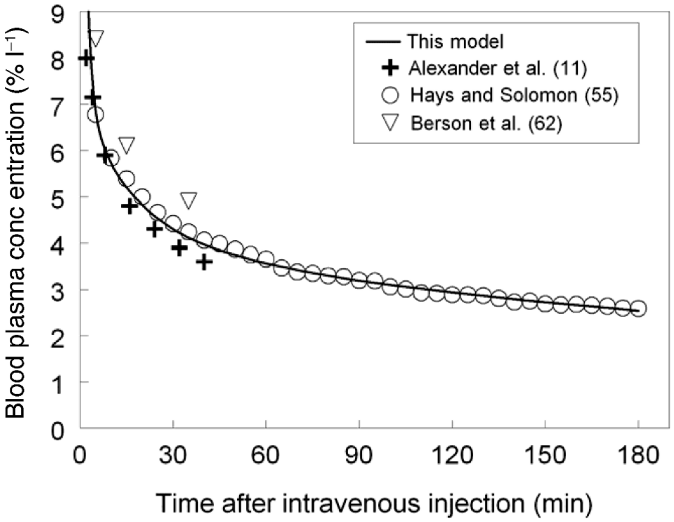

FIG. 10. Model predictions of disappearance of intravenously injected radioiodine from plasma compared with central values determined in three studies (*11, 55, 62*).

ments varied by less than 15% from the estimated medians. The plus signs in Figs. 10 and 13 were determined from graphs of mean values for 9–10 euthyroid subjects (*11*); variability of measurements was not reported. The closed circles in Figs. 12 and 13 represent means for 34 euthyroid patients (*141*); vertical lines through the circles represent standard deviations.

The model predictions shown in Fig. 10 are for total blood iodide. The comparison with observed values assumes equilibration between blood plasma and RBC water. The model simulation in Fig. 11 assumes no reabsorption of secreted ^{131}I to blood because the measurements required removal of salivary and gastric

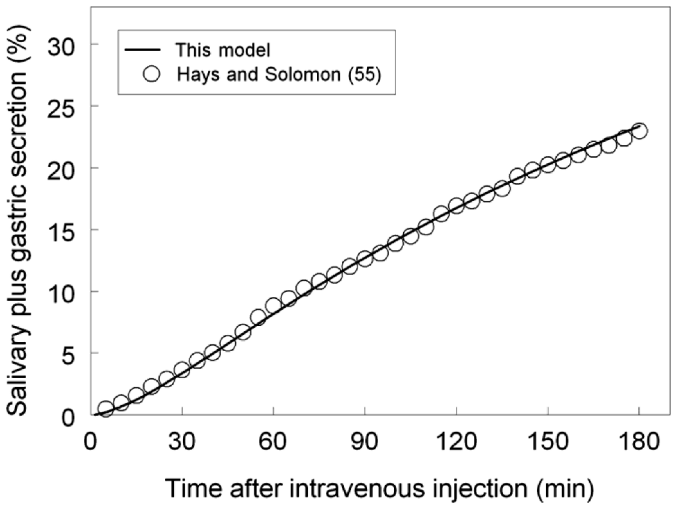

FIG. 11. Model predictions of cumulative secretion of intravenously injected ^{131}I in saliva and gastric juice compared with means of observed values for a group of healthy young adult males (*55*). The model simulation was based on the assumption that there was no absorption of salivary or gastric secretions to blood because observations required removal of these secretions from the body.

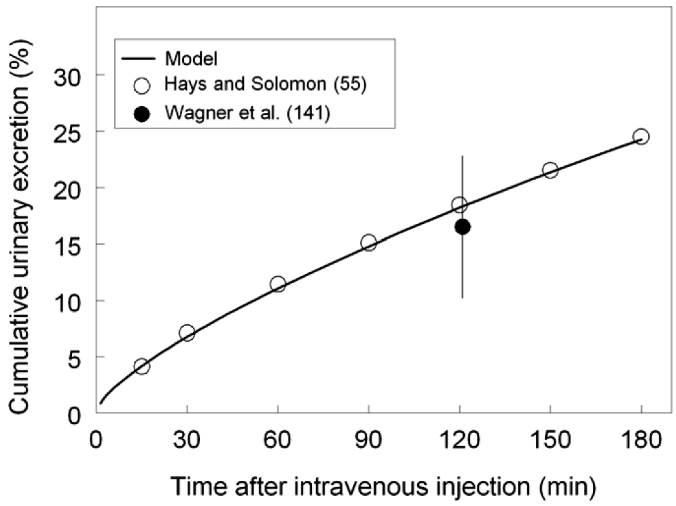

FIG. 12. Model predictions of cumulative urinary excretion of ^{131}I after intravenous injection compared with mean values determined for two study groups (*55, 141*).

secretions through a nasogastric tube. In Fig. 12, the predicted cumulative urinary excretion of ^{131}I at a given time includes the amount in the urinary bladder contents.

In Fig. 13 the observations are compared with model-generated curves based on three different values of the transfer coefficient from Blood 1 to Thyroid 1. This transfer coefficient is derived from Eq. (2) and depends on the ratio Y/S, where Y is dietary stable iodine (μg day^{-1}) and S is daily secretion of hormonal iodine by the thyroid (μg day^{-1}). Estimates of Y and S were not reported for the three study groups addressed in the figure. The group represented by plus signs (*11*) was from a region with relatively low dietary iodine, suggesting a ratio Y/S less than the baseline value 2.5. The transfer coefficient based on the ratio Y/S = 2 yields

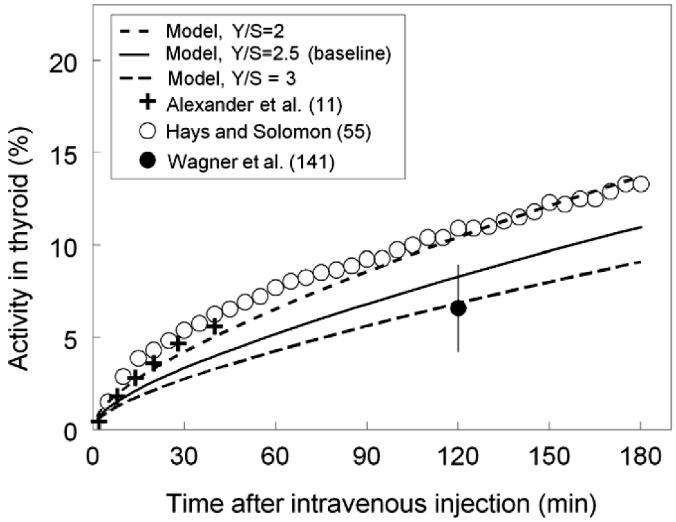

FIG. 13. Model predictions of thyroidal uptake of intravenously injected ^{131}I compared with mean values of external measurements for three study groups (*11, 55, 141*).

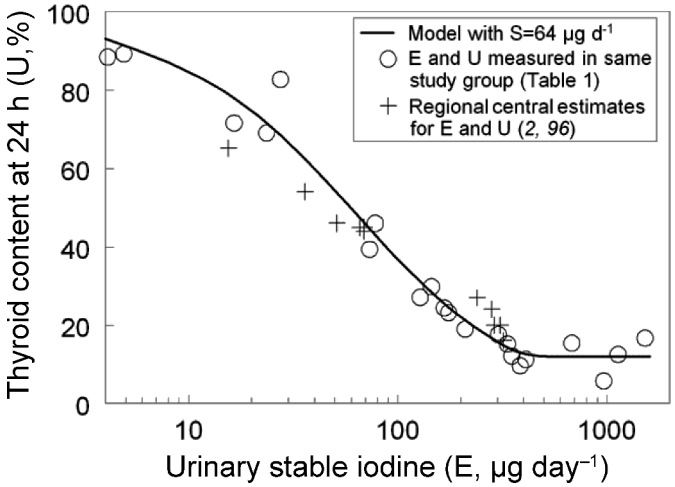

FIG. 14. Model predictions and observations of 24-h uptake of radioiodine by thyroid (U) as a function of daily urinary excretion of stable iodine (E). Values for E and U in same study group are from Table 1. Regional estimates of E and U are from refs. (*2, 96*).

TABLE 4
Model Predictions of Mass or Concentration of Stable Iodine in Tissues and Fluids at Equilibrium

	Dietary iodine (μg day^{-1})/thyroidal secretion of organic iodine (μg day^{-1})			
Quantity	130/52[a]	160/64[a]	190/76[a]	300/100[b]
Iodine in thyroid (μg)	6750	8310	9870	13,000
Iodide in blood plasma (μg dl^{-1})	0.22	0.27	0.32	0.51
Total extrathyroidal inorganic iodide (μg)	58	71	84	135
Organic iodine in blood plasma (μg dl^{-1})	4.3	5.2	6.2	8.2
Total extrathyroidal organic iodine (μg)	520	640	760	1000

[a] Baseline transfer coefficient describing thyroidal uptake (7.26 day^{-1}) is applied because the ratio of daily intake of iodine Y to daily thyroidal secretion S is 2.5.
[b] Transfer coefficient from Blood iodide to Thyroid iodide is 5.96 day^{-1} based on Eq. (2).

reasonable agreement with thyroidal uptake data for that group as well as data for the healthy young adult male subjects of Hays and Solomon (*55*) (open circles). Short-term urinary data for the third group, represented by the single closed circle, indicate mean iodine intake of the order of 200 μg day^{-1}, suggesting a ratio Y/S greater than 2.5. The transfer coefficient based on the ratio Y/S = 3 is consistent with the mean 2-h thyroidal uptake for that group.

Model predictions of the percentage of ingested radioiodine in the thyroid at 24 h after intake (U) assuming no radioactive decay are compared in Fig. 14 with observed values for subjects with different levels of stable iodine in urine (E). The measurements of E and U in the same study groups are from Table 1, and regional comparisons are from reviews by Zvonova (*96*) and Delange and Dunn (*2*). Model predictions are based on the transfer coefficients in Table 3 except that the transfer coefficient from Blood 1 to Thyroid 1 was varied with E as described by Eq. (3), down to a minimum value of 2.5 day^{-1}. For this comparison the value S was set at the sex-averaged reference value of 64 μg day^{-1}.

The model with baseline parameter values (Table 3) predicts that the thyroid contains about 29% of ingested or intravenously injected iodine at 24 h after intake, assuming no radioactive decay. The content of the thyroid is predicted to peak at about 30% of the ingested or injected amount during the period 24–48 h after intake.

Model predictions of the equilibrium content of iodine in the thyroid, concentration of inorganic iodide and organic iodine in blood, and total extrathoracic contents of inorganic iodide and organic iodide are listed in Table 4 for different combinations of dietary iodine Y and thyroidal secretion rate S. The predicted values are within the ranges of reported values for euthyroid subjects.

5. COMPARISON OF DERIVED DOSE COEFFICIENTS WITH ICRP VALUES

Dose coefficients for selected iodine isotopes based on the proposed model were compared with values based on the models and methods of ICRP Publication 68, *Dose Coefficients for Intakes of Radionuclides by Workers* (*18*). A dose coefficient is an absorbed dose per becquerel (Bq) intake by intravenous injection, inhalation or ingestion (1 Bq = 1 disintegration per second). The derivations of the alternate sets of dose coefficients differed only with regard to the systemic biokinetic model applied, i.e., the current ICRP systemic model for occupational intake of radioiodine (Fig. 1) or the proposed systemic model for iodine (Fig. 9 and Table 3). The respiratory model used in ICRP Publication 68 was applied in both sets of calculations of inhalation dose coefficients, and the gastrointestinal transit model used in ICRP Publication 68 was applied in both sets of calculations of injection, inhalation or ingestion dose coefficients. Absorbed dose estimates were made using the DCAL (Dose and Risk Calculation) software (*142*), which has been used since the early 1990s for calculation or quality assurance of the ICRP's dose coefficients for occupational and environmental intake of radionuclides. Intravenously injected activity was assumed to be in the form of inorganic iodide, inhaled activity was assumed to be in the form of elemental iodine [see respiratory model on page 22 of ref. (*18*)], and ingested radioiodine was assumed to be in soluble form and to be absorbed from the small intestine to blood as inorganic iodide. A gastrointestinal absorption fraction of 0.99 was applied in all cases.

TABLE 5
Comparison of Absorbed Dose per Unit Intake of Radioiodine by an Adult Male Based on the Proposed Model and the ICRP's Current Systemic Model for Workers (*18, 19*)

		Ratio of absorbed doses, proposed model:current ICRP model					
Isotope	Half-life	Thyroid	Stomach wall	Salivary glands	Kidneys	Liver	Other (mean)
Intravenous injection of iodide							
^{122}I	3.63 min	3.2	5.1	5.4	5.7	1.1	1.1
^{124}I	4.18 days	1.0	8.3	2.4	3.9	1.5	1.0
^{125}I	59.4 days	1.1	3.1	1.8	4.5	4.3	0.8
^{129}I	1.6×10^7 years	1.2	1.7	1.1	5.4	5.2	0.7
^{131}I	8.02 days	1.0	9.7	2.4	5.1	2.3	1.0
^{132}I	2.3 h	1.2	12	8.5	5.3	1.2	1.1
^{134}I	52.5 min	1.5	9.9	8.5	5.6	1.2	1.1
Inhalation of elemental iodine							
^{122}I	3.63 min	3.0	1.1	2.8	4.3	1.1	1.0
^{124}I	4.18 days	1.0	4.1	2.3	3.8	1.5	1.0
^{125}I	59.4 days	1.1	2.5	1.8	4.5	4.3	0.8
^{129}I	1.6×10^7 years	1.2	1.6	1.1	5.4	5.2	0.7
^{131}I	8.02 days	1.0	4.6	2.4	5.0	2.2	1.0
^{132}I	2.3 h	1.2	2.6	7.0	4.8	1.2	1.0
^{134}I	52.5 min	1.5	1.8	6.4	4.7	1.2	1.0
Ingestion in soluble form							
^{122}I	3.63 min	3.2	1.0	2.6	1.5	1.0	1.0
^{124}I	4.18 days	1.0	2.1	2.4	3.6	1.5	1.0
^{125}I	59.4 days	1.1	1.8	1.8	4.5	4.3	0.8
^{129}I	1.6×10^7 years	1.2	1.4	1.1	5.4	5.2	0.7
^{131}I	8.02 days	1.0	2.2	2.4	4.8	2.2	1.0
^{132}I	2.3 h	1.2	1.3	7.7	3.8	1.1	1.0
^{134}I	52.5 min	1.5	1.1	7.0	3.1	1.1	1.1

Results of the comparisons are illustrated in Table 5. The absorbed dose to the tissue identified as "Other" in Table 5 was calculated as the average of derived absorbed doses to adrenals, urinary bladder wall, bone surface, brain, breasts, small intestine wall, colon, muscle, ovaries, pancreas, red marrow, skin, spleen, testes, gallbladder wall, heart wall, uterus and lung. Compared with the ICRP's current model, the proposed model yields similar estimates of absorbed dose to the thyroid for isotopes with half-life of at least a few hours but generally higher estimates (up to a factor of 3.2) for shorter-lived isotopes. For most iodine isotopes the proposed model yields substantially higher estimates of absorbed dose to stomach wall, salivary glands and kidneys than does the ICRP model. The two models yield broadly similar absorbed dose estimates for remaining tissues, including liver, for isotopes with half-life up to a few days. The proposed model yields noticeably higher estimates of absorbed dose to liver for relatively long-lived iodine isotopes, particularly ^{125}I and ^{129}I. This is because a long radiological half-life is required for significant thyroidal release of activity to blood as thyroid hormones, which are depicted in this model as having high uptake by liver.

Dose coefficients for intravenous injection of ^{131}I-labeled T_4, T_3 or rT_3 based on the proposed model were compared with values for the adult listed in ICRP Publication 53, *Radiation Dose to Patients from Radiopharmaceuticals* (*26*), for the case of complete blocking of the thyroid. Recall that complete blocking is represented in the proposed model as prevention of transfer from Thyroid 1 to Thyroid 2 rather than prevention of entry into the thyroid as assumed in ICRP Publication 53. The transfer coefficients in the proposed model that describe the movement of extrathyroidal organic iodine are based on data for the relatively long-lived T_4, which represents the preponderance of extrathyroidal organic iodine. Thus, for application of the model to the case of intravenous injection of labeled T_4, it is not necessary to adjust any of the baseline transfer coefficients. In this case the model is implemented by assigning 1 Bq of the label to Blood 2 (organic iodine in blood) at time zero and tracking the activity associated with extrathyroidal organic iodine, including the activity gradually released to the blood iodide pool due to deiodination of thyroid hormones. The biokinetics of each of the shorter-lived hormones T_3 and rT_3 differs from that of T_4 and hence is not well represented by the baseline transfer coefficients describing the movement of extrathyroidal organic iodine. For the case of intravenous injection of labeled T_3 or rT_3 it is necessary to append additional blood, liver, kidney, ECF and other tissue compartments to the model structure and assign associated transfer coefficients specific to T_3 or rT_3. For example, these additional compartments could be called Blood 3, Liver 3, Kidney 3, Other 5 and Other 6, respectively. The transfer coefficients associated with these additional compartments are

TABLE 6
Comparison of Absorbed Dose Coefficients for Intravenous Injection of ^{131}I-Labeled T_4, T_3 or rT_3 into an Adult Male Based on the Proposed Model with Values Listed in ICRP Publication 53 (*26*)[a]

	Absorbed dose coefficient based on proposed model as multiple of value listed in ICRP Publication 53					
Form	Thyroid	Stomach wall	Salivary glands[b]	Kidneys	Liver	Red marrow
T_4	3.6	1.2	0.91	7.1	7.8	0.89
T_3	20	4.0	2.9	3.1	2.5	0.85
rT_3	69	11	7.9	3.9	2.7	1.1

[a] Assuming blocked thyroid, implemented in the proposed model by assigning transfer coefficient of zero from inorganic iodide to organic iodine compartment of thyroid (Thyroid 1 to Thyroid 2) and in ICRP Publication 53 by assuming no entry of ^{131}I into the thyroid.
[b] Salivary glands not addressed explicitly in ICRP Publication 53.

listed in Table 2. The proposed model is implemented in the case of injection of labeled T_3 or rT_3 by assigning 1 Bq of the label to the Blood 3 pool at time zero. Once the activity reaches Blood 1 or Colon contents, it is assumed to follow the kinetics defined in Table 3.

Results of the comparison of dose coefficients for intravenous injection of T_4, T_3 or rT_3 are shown in Table 6. Comparisons are in terms of ratios of dose coefficients based on the proposed model to corresponding values in Publication 53. The dose coefficients based on the present model are substantially higher than values in Publication 53 for thyroid, kidneys and liver for all three forms of ^{131}I and for stomach wall and salivary glands for ^{131}I-labeled T_3 and rT_3. The reasons for the differences from values in Publication 53 are not entirely clear, because the biokinetic model used in that document is not fully explained. The model used in Publication 53 is said to be similar to that of Hays (*25*), but the uniformity of dose coefficients in Publication 53 indicates that activity was assumed to be uniformly distributed in all tissues, whereas Hays assigned greater activity concentrations to liver and kidneys than to other tissues. The differences in dose coefficients for stomach wall and salivary glands appear to be due to a detailed tracking of activity released to blood iodide in the present model but not in the model of Publication 53. The differences in dose coefficients for thyroid are also due in part to the more detailed tracking of inorganic iodide in the present model but, more importantly, to the different representations of thyroid blocking in the two models. In the present model the blocked thyroid accumulates inorganic iodide and retains it briefly, returning it to blood at the rate 36 day^{-1}. In the model of ICRP Publication 53, thyroid blocking is interpreted as a lack of entry of inorganic iodide into the thyroid.

SUMMARY

The proposed biokinetic model for iodine consolidates and extends existing physiological systems models describing three subsystems of the iodine cycle in the human body: (1) circulating inorganic iodide; (2) thyroidal iodine, including trapping and organic binding of iodide and synthesis, storage, and secretion of thyroid hormones; and (3) extrathyroidal organic iodine. The proposed model accounts for the influence of dietary stable iodine as well as the level of thyroid hormone secretion on the biokinetics of iodine, provides a relatively detailed description of the early biokinetics of absorbed iodine aimed at improving radiation dose estimates for short-lived isotopes of iodine, and provides a model of the thyroid intended for dosimetry of radioiodine during thyroid blocking. The model may be adapted to a number of special problems in radiation protection by modification of the baseline transfer coefficients or addition of compartments that exchange inorganic iodide or organic iodine with blood. For example, a compartment representing mammary glands could be added to address transfer of radioiodine from the lactating mother to the nursing infant. Compartments representing the fetus could be added to address fetal doses due to transfer of radioiodine from the mother to the fetus.

Baseline transfer coefficients are provided in this paper for reference workers or adult members of the public with typical iodine intake and thyroid hormone secretion rate. Compared with the ICRP's current iodine model for workers (Fig. 1), the proposed model yields similar estimates of absorbed dose to thyroid per unit uptake to blood for relatively long-lived iodine isotopes but noticeably higher estimates of thyroid dose for short-lived iodine isotopes. For most iodine isotopes the proposed model yields substantially higher estimates of absorbed dose to stomach wall, salivary glands and kidneys per unit uptake to blood than does the current ICRP model. The proposed model and current ICRP model yield broadly similar absorbed dose estimates for remaining tissues for most iodine isotopes. Exceptions are ^{125}I and ^{129}I, which have sufficiently long half-lives that the proposed model's projection of a relatively high accumulation of thyroid hormones in liver results in elevated estimates of absorbed dose to liver.

Dose coefficients for intravenous injection of ^{131}I-labeled thyroid hormones based on the proposed model are substantially higher than values in ICRP Publication 53 (*26*) for the thyroid, kidneys, liver, stomach wall and salivary glands for adult patients with blocked thyroid. The differences in dose coefficients for the non-thyroidal organs are due to the more detailed tracking of extrathyroidal organic iodine and released inorganic iodide in the present model. The differences in coeffi-

cients for the blocked thyroid are due in part to the more detailed tracking of activity in the present model but, more importantly, to a different representation of thyroid blocking. In the present model the blocked thyroid accumulates inorganic iodide and retains it briefly. In the model of ICRP Publication 53, thyroid blocking is interpreted as a lack of entry of inorganic iodide into the thyroid.

The proposed model was developed as part of a study by the U.S. Nuclear Regulatory Commission (NRC) of the influence of dietary stable iodine on doses from intake of radioiodine.[2] Analyses to this point support the widely held view that the absorbed dose to the thyroid from ^{131}I or longer-lived iodine isotopes is not strongly sensitive to the level of stable iodine in diet, at least for levels of dietary stable iodine reported for the U.S. in recent years. Subsequent publications are planned to address this issue as well as the age-specific biokinetics of iodine and dose reduction due to thyroid blocking.

ACKNOWLEDGMENT

This work was supported by the U.S. Nuclear Regulatory Commission Office of Nuclear Regulatory Research under Inter-agency Agreement number DOE 1886-T249-06/1886-T233-06 and was prepared by Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Department of Energy under contract DE-AC05-00OR22725.

Received: April 14, 2010; accepted: June 29, 2010; published online: August 12, 2010

REFERENCES

1. R. D. Utiger, Thyroid diseases. In *Endocrinology and Metabolism, Fourth Edition* (P. Felig and L. A. Frohman, Eds.), pp. 259–348. McGraw-Hill, New York, 2001.
2. F. M. Delange and J. T. Dunn, Iodine deficiency. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, Ninth Edition* (S. C. Werner, S. H. Ingbar and L. E. Braverman, Eds.), pp. 264–288. Lippincott Williams & Wilkins, New York, 2005.
3. BEST (Board on Environmental Studies and Toxicology), *Health Implications of Perchlorate Ingestion*. National Academy Press, Washington, DC, 2005.
4. G. L. Brownell, Analysis of techniques for the determination of thyroid function with radioiodine. *J. Clin. Endocrinol*. **11**, 1095–1105 (1951).
5. D. S. Riggs, Quantitative aspects of iodine metabolism in man. *Pharmacol. Rev*. **4**, 284–370 (1952).
6. T. H. Oddie, I. Meschan and J. Wortham, Thyroid function assay with radioiodine. I. Physical basis of study of early phase of iodine metabolism and iodine uptake. *J. Clin. Invest*. **34**, 95–105 (1955).
7. M. T. Hays and L. H. Wegner, A mathematical and physiological model for early distribution of radioiodine in man. *J. Appl. Physiol*. **20**, 1319–1328 (1965).
8. M. Berman, E. Hoff, M. Barandes, D. V. Becker, M. Sonnenberg, R. Benua and D. A. Koutras, Iodine kinetics in man – a model. *J. Clin. Endocrinol. Metab*. **28**, 1–14 (1968).
9. J. T. Nicoloff and J. T. Dowling, Estimation of thyroxine distribution in man. *J. Clin. Invest*. **47**, 26–37 (1968).
10. L. J. DeGroot, P. Decostre and R. Phair, A mathematical model of human iodine metabolism. *J. Clin. Endocr*. **32**, 757–765 (1971).
11. W. D. Alexander, J. Shimmins, J. W. Robertson, P. W. Horton, D. G. McLarty and R. M. Harden, Radioisotope studies of thyroid function and thyroid hormone metabolism. In *Dynamic Studies with Radioisotopes in Medicine. Proceedings of a symposium. Rotterdam, 31 Aug–4 Sept, 1970*, pp. 179–190. IAEA, Vienna, 1971.
12. R. A. McGuire and M. T. Hays, A kinetic model of human thyroid hormones and their conversion products. *J. Clin. Endocrinol. Metab*. **53**, 852–862 (1981).
13. J. P. Bazin, P. Fragu, R. Di Paola, M. Di Paola and M. Tubiana, Early kinetics of thyroid trap in normal human patients and in thyroid diseases. *Eur. J. Nucl. Med*. **6**, 317–326 (1981).
14. M. Degon, S. Chipkin, C. V. Hollot, T. Zoeller and Y. Chait, A computational model of the human thyroid. *Math. Biosci*. **212**, 22–53 (2008).
15. M. Balonov, G. Kaidanovsky, I. Zvonova, A. Kovtun, A. Bouville, N. Luckyanov and P. Voilleque, Contributions of short-lived radioiodines to thyroid doses received by evacuees from the Chernobyl area estimated using early *in vivo* activity measurements. *Radiat. Prot. Dosimetry* **105**, 593–599 (2003).
16. S. A. Book, D. A. McNeill, N. J. Parks and W. L. Spangler, Comparative effects of iodine-131 and iodine-132 in rat thyroid glands. *Radiat. Res*. **81**, 246–253 (1980).
17. I. Ya. Vasilenko, Radiation hazard of iodine isotopes. *Sov. At. Energy* **63**, 751–756 (1988). [Translated from *Atomnaya Energiya* **63**, 244–248 (1987)]
18. ICRP, *Dose Coefficients for Intakes of Radionuclides by Workers*. Publication 68, *Annals of the ICRP*, Vol. 24, No. 4, International Commission on Radiological Protection, Pergamon Press, Oxford, 1994.
19. ICRP, *Individual Monitoring for Internal Exposure of Workers. Replacement of ICRP Publication 54*. Publication 78, *Annals of the ICRP*, Vol. 27, No. 3/4, International Commission on Radiological Protection, Pergamon Press, Oxford, 1997.
20. J. W. Stather and J. R. Greenhalgh, *The Metabolism of Iodine in Children and Adults*. Report NRPB-R140, National Radiological Protection Board, Chilton, Didcot, 1983.
21. J. R. Johnson, A review of age dependent radioiodine dosimetry. In *Age-Related Factors in Radionuclide Metabolism and Dosimetry* (G. B. Gerber, H. Metivier and H. Smith, Eds.), pp. 249–260. Martinus Nijhoff, Dordrecht, 1987.
22. ICRP, *Age-dependent Doses to Members of the Public from Intake of Radionuclides, Part 1*. Publication 56, *Annals of the ICRP*, Vol. 20, No. 2, International Commission on Radiological Protection, Pergamon Press, Oxford, 1989.
23. MIRD, Summary of current radiation dose estimates to humans from ^{123}I, ^{124}I, ^{125}I, ^{126}I, ^{130}I, ^{131}I, and ^{132}I as sodium iodide. MIRD dose estimate report no. 5. *J. Nucl. Med*. **16**, 857–860 (1975).
24. J. S. Robertson and C. A. Gorman, Gonadal radiation dose and its genetic significance in radioiodine therapy of hyperthyroidism. *J. Nucl. Med*. **17**, 826–835 (1976).
25. M. T. Hays, Radiation dosimetry of radioiodinated thyroid hormones. *J. Nucl. Med*. **25**, 1068–1074 (1985).
26. ICRP, *Radiation Dose to Patients from Radiopharmaceuticals*. Publication 53, *Annals of the ICRP*, Vol. 18, No. 1–4, International Commission on Radiological Protection, Pergamon Press, Oxford, 1987.
27. L. Johansson, S. Leide-Svegborn, S. Mattsson and B. Nosslin, Biokinetics of iodide in man: Refinement of current ICRP dosimetry models. *Cancer Biother. Radiopharm*. **18**, 445–450 (2003).

[2] The model or other information contained in this paper has not been approved by the NRC for use in licensing or decision making.

28. V. Berkovski, Radioiodine biokinetics in the mother and fetus. Part 1. Pregnant woman. In *Radiation and Thyroid Cancer*, pp. 319–325. Publication No. EUR 18552 EN, World Scientific Publishing, Singapore, 1999.

29. V. Berkovski, Radioiodine biokinetics in the mother and fetus. Part 2. Fetus. In *Radiation and Thyroid Cancer*, pp. 327–332. Publication No. EUR 18552 EN, World Scientific Publishing, Singapore, 1999.

30. V. Berkovski, New iodine models family for simulation of short-term biokinetics processes, pregnancy and lactation. *Food Nutr. Bull*. **23**, 87–94 (2002).

31. ICRP, *Doses to the Embryo and Fetus from Intakes of Radionuclides by the Mother*. Publication 88, *Annals of the ICRP*, Vol. 31, No. 1–3, Pergamon Press, Oxford, 2002.

32. G. A. Adams and J. A. Bonnell, Administration of stable iodide as a means of reducing thyroid irradiation resulting from inhalation of radioactive iodine. *Health Phys*. **7**, 127–149 (1962).

33. D. Ramsden, F. H. Passant, C. O. Peabody and R. G. Speight, Radioiodine uptakes in the thyroid. Studies of the blocking and subsequent recovery of the gland following the administration of stable iodine. *Health Phys*. **13**, 633–646 (1967).

34. P. B. Zanzonico and D. V. Becker, Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by ^{131}I from radioactive fallout. *Health Phys*. **78**, 660–667 (2000).

35. WHO, *Assessment of the Iodine Deficiency Disorders and Monitoring Their Elimination. Second Edition*. Joint Publication of International Council for Control of Iodine Deficiency Disorders, United Nations Children's Fund, and World Health Organization (WHO). WHO/NHD/01.1, World Health Organization, Geneva, 2001.

36. FAO/WHO, Iodine. In *Human Vitamin and Mineral Requirements. Report of a Joint FAO/WHO Expert Consultation*, pp. 181–194. World Health Organization, Geneva, 2002.

37. R. M. Parr, H. Crawley, M. Abdulla, G. V. Iyengar and J. Kumpulainen, *Human Dietary Intakes of Trace Elements: A Global Literature Survey Mainly for the Period 1970–1991. Data Listing and References*. International Atomic Energy Agency, Vienna, 1992.

38. N. J. O'Hare, D. Murphy and J. F. Malone, Thyroid dosimetry of adult European populations. *Br. J. Radiol*. **71**, 535–543 (1998).

39. G. V. Iyengar, H. Kawamura, H. S. Dang, R. M. Parr, J. Wang, P. Akhter, S. Y. Cho, E. Natera, F. K. Miah and M. S. Nguyen, Dietary intakes of seven elements of importance in radiological protection by Asian population: Comparison with ICRP data. *Health Phys*. **86**, 557–564. (2004).

40. B. de Benoist, M. Andersson, I. Egli, B. Takkouche and H. Allen, Eds., *Iodine Status Worldwide. WHO Global Database on Iodine Deficiency*. Department of Nutrition for Health and Development, World Health Organization, Geneva, 2004.

41. K. L. Caldwell, R. Jones and J. G. Hollowell, Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001–2002. *Thyroid* **15**, 692–699 (2005).

42. T. H. Oddie, D. A. Fisher, W. M. McConahey and C. S. Thompson, Iodine intake in the United States: A reassessment. *J. Clin Endocrinol. Metab*. **30**, 659–665. (1970).

43. D. A. Fisher, T. H. Oddie and C. S. Thompson, Thyroidal thyronine and non-thyronine iodine secretion in euthyroid subjects. *J. Clin. Endocrinol. Metab*. **33**, 647–652 (1971).

44. M. Milakovic, G. Berg, E. Nystro, G. Lindstedt and M. Gebre-Medhin, Urinary iodine and thyroid volume in a Swedish population. *J. Internal Med*. **255**, 610–614 (2004).

45. R. Bilek, J. Bednar and V. Zamrazil, Spectrophotometric determination of urinary iodine by the Sandell-Kolthoff reaction subsequent to dry alkaline ashing. Results from the Czech Republic in the period 1994–2002. *Clin. Chem. Lab. Med*. **43**, 573–580 (2005).

46. K. D. Burman, Low iodine diets. In *Thyroid Cancer. A Comprehensive Guide to Clinical Management, Second Edition* (L. Wartofsky and D. Van Nostrand, Eds.), pp. 677–681. Human Press, Totowa, NJ, 2006.

47. CDC, *National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population 1999–2002*. U.S. Centers for Disease Control and Prevention, Atlanta, 2008. [Available online at http://www.cdc.gov/nutritionreport/index.html]

48. B. N. E. Cohn, Absorption of compound solution of iodine from the gastro-intestinal tract. *Arch. Intern. Med*. **49**, 950–956 (1932).

49. WHO, Iodine. In *Toxicological Evaluation of Certain Food Additives and Contaminants*. WHO Food Additives Series, No. 24, World Health Organization, Cambridge University Press, Cambridge, UK, 1989. [Available online at http://www.inchem.org/documents/jecfa/jecmono/v024je11.htm]

50. M. D. Small, A. Bezman, A. E. Longarni, A. Fennell and N. Zamcheck, Absorption of potassium iodide from gastro-intestinal tract. *Proc. Soc. Exp. Biol. Med*. **106**, 450–452 (1961).

51. F. R. Keating, Jr. and A. Albert, The metabolism of iodine in man as disclosed with the use of radioiodine. *Rec. Progr. Hormone Res*. **4**, 429–481 (1948).

52. T. H. Oddie, D. A. Fisher and J. M. Long, Factors affecting the estimation of iodine entering the normal thyroid gland using short-term clearance studies. *J. Clin. Endocrinol. Metab*. **24**, 924–933 (1964).

53. D. A. Fisher, T. H. Oddie and D. Epperson, Effect of increased dietary iodide on thyroid accumulation. *J. Clin. Endocrinol. Metab*. **25**, 1580–1590 (1965).

54. E. J. Wayne, D. A. Koutras and W. D. Alexander, *Clinical Aspects of Iodine Metabolism*. F. A. Davis Co., Philadelphia, 1964.

55. M. T. Hays and D. H. Solomon, Influence of the gastrointestinal iodide cycle on the early distribution of radioactive iodide in man. *J. Clin. Invest*. **44**, 117–127 (1965).

56. N. B. Myant, B. D. Corbett, A. J. Honour and E. E. Pochin, Distribution of radioiodide in man. *Clin. Sci*. **9**, 405–419 (1950).

57. R. M. Harden and W. D. Alexander, The salivary iodide trap in man: Clinical applications. *Proc. R. Soc. Med*. **61**, 647–649 (1968).

58. R. M. Harden, W. D. Alexander, J. Shimmins and D. Chisholm, A comparison between the gastric and salivary concentration of iodide, pertechnetate, and bromide in man. *Gut* **10**, 928–930 (1969).

59. P. P. A. Smyth and L. H. Duntas, Iodine uptake and loss – Can frequent strenuous exercise induce iodine deficiency? *Horm. Metab. Res*. **37**, 555–558 (2005).

60. N. S. Bricker and C. J. Hlad, Observations on the mechanism of the renal clearance of ^{131}I. *J. Clin. Invest*. **34**, 1057–1072 (1955).

61. S. Vadstrup, Comparative aspects of iodine conservation in mammals. *Comp. Biochem. Physiol*. **106A**, 15–17 (1993)

62. S. A. Berson, R. S. Yalow, J. Sorrentino and B. Roswit, The determination of thyroidal and renal plasma ^{131}I clearance rates as a routine diagnostic test of thyroid dysfunction. *J. Clin. Invest*. **31**, 141–158 (1952).

63. T. H. Oddie, J. H. Meade and D. A. Fisher, An analysis of published data on thyroxine turnover in human subjects. *J. Clin. Endocrinol. Metab*. **26**, 425–436 (1966).

64. G. K. Korolev, Distribution of iodine-132 and tellurium-132 in the body of rats under intravenous administration. In *Radioactive Isotopes and the Body* (Yu. I. Moskalev, Ed.), Ed.), pp. 175–185. Izdatel'stvo Meditsina, AEC-tr-7195, 1969.

65. E. J. Esposito, ^{131}I concentration in submaxillary glands and other tissues of rats. *J. Dent. Res*. **49**, 459 (1970).

66. E. Dadachova, B. Bouzahzah, L. S. Zuckier and R. G. Pestell, Rhenium-188 as an alternative to iodine-131 for treatment of breast tumors expressing the sodium/iodide symporter (NIS). *Nucl. Med. Biol*. **29**, 13–18 (2002).

67. W. R. Ruegamer, The kinetics of ^{131}I metabolism in the dog and human. *Arch. Biochem. Biophys*. **47**, 119–136 (1953).

68. D. D. Ulmer, L. B. Perkins and J. G. Kereiakes, Alterations in iodine-131 distribution in the rat after whole-body x-irradiation. *Radiat. Res*. **11**, 810–819 (1959).

69. Yu. I. Moskalev and G. M. Yegorova, Distribution of iodine-131 in the rat organism following separate and combined exposure to this isotope and cobalt-60 gamma rays. In *Biological Effects of Radiation from External and Internal Sources* (Yu. I. Moskalev and V. S. Kalistratova, Eds.), pp. 116–122. Meditsina, AEC-tr-7457, 1972.

70. K. S. Kolbert, K. S. Pentlow, J. R. Pearson, A. Sheikh, R. D. Finn, J. L. Humm and S. M. Larson, Prediction of absorbed dose to normal organs in thyroid cancer patients treated with ^{131}I by use of ^{124}I PET and 3-dimensional internal dosimetry software. *J. Nucl. Med*. **48**, 143–149 (2007).

71. ICRP, *Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values*. Publication 89, *Annals of the ICRP*, Vol. 32, No. 3–4, International Commission on Radiological Protection, Pergamon Press, Oxford, 2002.

72. ICRP, *Human Alimentary Tract Model for Radiological Protection*. Publication 100, *Annals of the ICRP*, Vol. 36, No. 1–2, International Commission on Radiological Protection, Pergamon Press, Oxford, 2006.

73. P. Kopp, Thyroid hormone synthesis. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, Ninth Edition* (S. C. Werner, S. H. Ingbar, L. E. Braverman and R. D. Utiger, Eds.), pp. 52–76. Lippincott Williams & Wilkins, New York, 2005.

74. L. E. Braverman and S. H. Ingbar, Changes in thyroidal function during adaptation to large doses of iodide. *J. Clin. Invest*. **42**, 1216–1231 (1963).

75. S. A. Berson and R. S. Yalow, The iodide trapping and binding functions of the thyroid. *J. Clin. Invest*. **34**, 186–204 (1955).

76. J. W. K. Robertson, J. Shimmins, P. W. Horton, J. H. Lazarus and W. D. Alexander, Determination of the rates of accumulation and loss of iodide and of protein binding of iodine in the human thyroid gland. In *Dynamic Studies with Radioisotopes in Medicine. Proceedings of a symposium. Rotterdam, 31 Aug–4 Sept, 1970*, pp. 199–210. IAEA, Vienna, 1971.

77. F. S. Greenspan, The thyroid gland. In *Basic and Clinical Endocrinology, Seventh Edition* (F. S. Greenspan and D. G. Gardner, Eds.), pp. 215–233. McGraw-Hill, New York, 2004.

78. A. C. Bianco and P. R. Larsen, Intracellular pathways of iodothyronine metabolism. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, Ninth Edition* (S. C. Werner, S. H. Ingbar, L. E. Braverman and R. D. Utiger, Eds.), pp. 109–134. Lippincott Williams & Wilkins, New York, 2005.

79. D. A. Fisher and T. H. Oddie, Thyroidal radioiodine clearance and thyroid iodine accumulation: Contrast between random daily variation and population data. *J. Clin. Endocrinol. Metab*. **29**, 111–115 (1969).

80. A. Taurog, Hormone synthesis. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. Seventh Edition* (L. L. Braverman and R. D. Utiger, Eds.), pp. 47–81. J. B. Lippincott, Philadelphia, 1996.

81. S. Nomura, C. S. Pittman, J. B. Chambers, M. W. Buck and T. Shimizu, Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. *J. Clin. Invest*. **56**, 643–652 (1975).

82. J. C. Choufoer, M. van Rhijn, A. A. Kassenaar and A. Querido, Endemic goiter in Western New Guinea: Iodine metabolism in goitrous and nongoitrous subjects. *J. Clin. Endocrinol. Metab*. **23**, 1203–1218 (1963).

83. D. D. Adams, T. H. Kennedy, J. C. Choufoer and A. Querido, Endemic goiter in Western New Guinea. III. Thyroid-stimulating activity of serum from severely iodine-deficient people. *J. Clin. Endocrinol. Metab*. **28**, 685–692 (1968).

84. J. B. Stanbury, G. L. Brownell, D. L. Riggs, H. Perinetti, J. Itoiz and E. B. del Castillo, *Endemic Goiter. The Adaptation of Man to Iodine Deficiency*. Harvard University Press, Cambridge, MA, 1954.

85. A. M. Ermans, J. E. Dumont and P. A. Bastenie, Thyroid function in goiter endemic: I. Impairment of hormone synthesis and secretion in the goitrous gland. *J. Clin. Endocrinol. Metab*. **23**, 539–549 (1963).

86. S. H. Ingbar and N. Freinkel, Simultaneous estimation of rates of thyroxine degradation and thyroid hormone synthesis. *J. Clin. Invest*. **34**, 808–819 (1955).

87. J. F. Colard, W. G. Verly, J. A. Henry and R. R. Boulenger, Fate of the iodine radioisotopes in the human and estimation of the radiation exposure. *Health Phys*. **11**, 23–35 (1965).

88. L. J. DeGroot, Kinetic analysis of iodine metabolism. *J. Clin. Endocrinol*. **26**, 149–173 (1966).

89. S. Ohtaki, S. Moriya, H. Suzuki and Y. Horiuchi, Nonhormonal iodine escape from the normal and abnormal thyroid gland. *J. Clin. Endocrinol. Metab*. **27**, 728–740 (1967).

90. S. Nagataki, K. Shizume and K. Nakao, Thyroid function in chronic excess iodide ingestion: Comparison of thyroidal absolute iodine uptake and degradation of thyroxine in euthyroid Japanese subjects. *J. Clin. Endocrinol*. **27**, 638–647 (1967).

91. J. C. Nelson, A. Renschler and J. W. Dowswell, The normal thyroidal uptake of iodine. *Calif. Med*. **112**, 11–14 (1970).

92. R. H. Caplan, R. Kujak, S. Murvich, O. Hicks, W. Frank and G. A. Gundersen, Current status of the radioactive ^{131}I uptake test: Effects of gelatin capsules and dietary iodine. *Minn. Med*. **59**, 530–535 (1976).

93. P. L. Hooper, B. A. Rhodes and M. J. Conway, Exercise lowers thyroid radioiodine uptake. *J. Nucl. Med*. **21**, 835–837 (1980).

94. J. A. Pittman, G. E. Dailey and R. J. Beschi, Changing normal values for thyroidal radioiodine uptake. *N. Engl. J. Med*. **280**, 1431–1434 (1969).

95. A. M. Ermans, Iodine kinetics in iodine deficiency. In *Iodine Deficiency in Europe: A Continuing Concern* (F. Delange, J. T. Dunn and D. Glinoer, Eds.), pp. 51–56. Plenum, New York, 1993.

96. I. A. Zvonova, Dietary intake of stable I and some aspects of radioiodine dosimetry. *Health Phys*. **57**, 471–475 (1989).

97. D. A. Koutras, W. D. Alexander, R. M. Harden and E. Wayne, Effect of small iodine supplements on thyroid function in normal individuals. *J. Clin. Endocrinol. Metab*. **24**, 857–862 (1964).

98. M. T. Harrison, Iodine balance in man. *Postgrad. Med. J*. **44**, 69–71, 1968.

99. D. A. Fisher and T. H. Oddie, Comparison of thyroidal iodine content and turnover in euthyroid subjects: Validity of estimation of thyroid iodine accumulation from short-term clearance studies. *J. Clin. Endocrinol. Metab*. **29**, 721–727 (1969).

100. P. Hellstern, H. E. Keller, B. Weinheimer and H. Wesch, Thyroid iodine concentration and total thyroid iodine in normal subjects and in endemic goiter subjects. *Clin. Endocrinol*. **9**, 351–356 (1978).

101. J. Handl, W. Kuehn and R. D. Hesch, Content and heterogeneity of distribution of iodine in human and bovine thyroid glands determined by neutron activation analyses. *J. Endocrinol. Invest*. **7**, 97–101 (1984).

102. B. Shapiro, B. Shulkin, M. Gross and L. Troncone, Thyroid imaging with radiopharmaceuticals. In *Thyroid Diseases. Basic Science, Pathology, Clinical and Laboratory Diagnoses* (L. Troncone, B. Shapiro, M. Satta and F. Monaco, Eds.), pp. 274–292, CRC Press, Boca Raton, FL, 1994.

103. M. T. Hays, Estimation of total body iodine content in normal young men. *Thyroid* **7**, 671–675 (2001).

104. J. T. Nicoloff, A new method for the measurement of thyroidal iodine release in man. *J. Clin. Invest*. **49**, 1912–1921 (1970).

105. N. V. Bhagavan, *Medical Biochemistry, Fourth Edition*, pp. 769–781. Academic Press, New York, 2001.

106. S. A. Berson and R. S. Yalow, Quantitative aspects of iodine metabolism. The exchangeable organic iodine pool, and the rates of thyroidal secretion, peripheral degradation and fecal excretion of endogenously synthesized organically bound iodine. *J. Clin. Invest*. **33**, 1533–1552 (1954).

107. R. I. Gregerman, G. W. Gaffney and N. W. Schock, Thyroxine turnover in euthyroid man with special reference to changes with age. *J. Clin. Invest*. **41**, 2065–2074 (1962).

108. J. S. Cobb, M. Adam, P. J. Pegg, P. M. Keane and J. C. Massey, Thyroid function in euthyroid Jamaicans. *J. Clin. Endocrinol. Metab*. **31**, 450–452 (1970).

109. K. E. Halnan, The metabolism of radioiodine and radiation dosage in man. *Br. J. Radiol*. **37**, 101–114 (1964).

110. E. J. Underwood, Iodine. In *Trace Elements in Human and Animal Nutrition, Fourth Edition*, pp. 271–301. Academic Press, New York, 1977.

111. T. H. Oddie, D. A. Fisher and D. Epperson, Effect of exogenous thyroxine on thyroid accumulation and secretion in euthyroid subjects. *J. Clin Endocrinol. Metab*. **25**, 1196–1206 (1965).

112. J. Herrmann, E. Heinen, H. J. Kroll, K. H. Rodorff and H. L. Krueskemper, Thyroid function and thyroid hormone metabolism in elderly people. *Klin. Wochenschr*. **59**, 315–323 (1981).

113. S. Mariotti, C. Franceschi, A. Cossarizza and A. Pinchera, The aging thyroid. *Endocr. Rev*. **16**, 686–715 (1995).

114. C. Sawin, Age-related changes in thyroid secretion. In *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, Ninth Edition* (S. C. Werner, S. H. Ingbar and L. E. Braverman, Eds.), pp. 214–219. Lippincott Williams & Wilkins, New York, 2005.

115. D. A. Fisher and T. H. Oddie, Comparison of thyroidal iodide accumulation and thyroxine secretion in euthyroid subjects. *J. Clin. Endocrinol. Metab*. **24**, 1143–1154 (1964).

116. T. H. Oddie, J. H. Meade, J. Myhill and D. A. Fisher, Dependence of renal clearance of radioiodide on sex, age and thyroidal status. *J. Clin. Endocrinol. Metab*. **26**, 1293–1296 (1966).

117. H. N. Wellman, J. G. Kereiakes and B. M. Branson, Total- and partial-body counting of children for radiopharmaceutical dosimetry data. In *Medical Radionuclides: Radiation Dose and Effects* (R. J. Cloutier, C. L. Edwards and W. S. Snyder, Eds.), pp. 133–156. U.S. Atomic Energy Commission, Oak Ridge, TN, 1970.

118. D. E. Dunning and G. Schwarz, Variability of human thyroid characteristics and estimates of dose from ingested ^{131}I. *Health Phys*. **40**, 661–675 (1981).

119. F. L. Bordell, J. A. Sayeg and N. Wald, In vivo measured effective half-life of ^{125}I in human thyroids. *Phys. Med. Biol*. **17**, 365–373 (1972).

120. R. G. Tucker and A. Keys, Concentration of serum protein-bound iodine in normal men. *J. Clin. Invest*. **30**, 869–873 (1951).

121. J. H. Oppenheimer, G. Bernstein and J. Hasen, Estimation of rapidly exchangeable cellular thyroxine from the plasma disappearance curves of simultaneously administered thyroxine-I-131 and albumin-I-125. *J. Clin. Invest*. **46**, 762–777 (1967).

122. C. S. Pittman, J. B. Chambers and V. H. Read, The extrathyroidal conversion rate of thyroxine to triiodothyronine in normal man. *J. Clin. Invest*. **50**, 1187–1196 (1971).

123. J. D. Acland, The interpretation of the serum protein-bound iodine: A review. *J. Clin. Pathol*. **24**, 187–218 (1971).

124. J. T. Nicoloff, J. C. Low, J. H. Dussault and D. A. Fisher, Simultaneous measurement of thyroxine and triiodothyronine peripheral turnover kinetics in man. *J. Clin. Invest*. **51**, 473–483 (1972).

125. K. Sterling, J. C. Lashof and E. B. Man, Disappearance from serum of I-131-labeled L-thyroxine and L-triiodothyronine in euthyroid subjects. *J Clin Invest*. **33**, 1031–1035 (1954).

126. K. Sterling, Radiothyroxine turnover studies in thyroid disease after therapy. *J. Clin. Invest*. **37**, 1348–1356 (1958).

127. E. J. Lennon, N. H. Engbring and W. W. Engstrom, Studies of the rate of disappearance of labeled thyroxine from the intravascular compartment. *Clin. Invest*. **40**, 996–1005 (1961).

128. R. R. Cavalieri and G. L. Searle, The kinetics of distribution between plasma and liver of ^{131}I-labeled L-thyroxine in man: Observations of subjects with normal and decreased serum thyroxine-binding globulin. *J. Clin. Invest*. **45**, 939–949 (1966).

129. L. Wartofsky, D. Martin and J. M. Earll, Alterations in thyroid iodine release and the peripheral metabolism of thyroxine during acute falciparum malaria in man. *J. Clin. Invest*. **51**, 2215–2232 (1972).

130. I. J. Chopra, An assessment of daily production and significance of thyroidal secretion of 3,3′,5′-triiodothyronine (reverse T_3) in man. *J. Clin. Invest*. **58**, 32–40 (1976).

131. M. T. Hays and R. A. McGuire, Distribution of subcutaneous thyroxine, triiodothyronine, and albumin in man : Comparison with intravenous administration using a kinetic mode. *J. Clin. Endocrinol. Metab*. **51**, 1112–1117 (1980).

132. R. R. Cavalieri, M. Steinberg and G. L. Searle, The distribution kinetics of triiodothyronine: Studies of euthyroid subjects with decreased plasma thyroxine-binding globulin and patients with Graves' disease. *J. Clin. Invest*. **49**, 1041–1050 (1970).

133. J. M. Hiss and J. T. Dowling, Thyroxine metabolism in untreated and treated pancreatic steatorrhea. *J. Clin. Invest*. **41**, 988–995 (1962).

134. M. Anbar, S. Guttman, G. Rodan and J. A. Stein, The determination of the rate of deiodination of thyroxine in human subjects. *J. Clin. Invest*. **44**, 1986–1991 (1965).

135. B. Busnardo and F. Casson, Aspects of fecal iodine excretion in man. *Acta Isot. (Padova)* **31**, 5–13 (1965).

136. M. Kirchgessner, J. He and W. Windisch, Homeostatic adjustments of iodine metabolism and tissue iodine to widely varying iodine supply in ^{125}I labeled rats. *J. Anim. Physiol. Anim. Nutr*. **82**, 238–250 (1999).

137. W. W. Winder and R. W. Heninger, Effect of exercise on tissue levels of thyroid hormones in the rat. *Am. J. Physiol*. **221**, 1139–1143 (1971).

138. M. Inada, K. Kasagi, S. Kurata, Y. Kazama, H. Takayama, K. Torizuka, M. Fukase and T. Soma, Estimation of thyroxine and triiodothyronine distribution and of the conversion rate of thyroxine to triiodothyronine in man. *J. Clin. Invest*. **55**, 1337–1348 (1975).

139. R. Bianchi, G. C. Zucchelli, D. Giannessi, A. Pilo, G. Mariani, A. Carpi and M. G. Toni, Evaluation of triiodothyronine (T_3) kinetics in normal subjects, in hypothyroid, and hyperthyroid patients using specific antiserum for the determination of labeled T_3 in plasma. *J. Clin. Endocrinol. Metab*. **46**, 203–214 (1978).

140. T. H. Oddie, J. H. Meade and D. A. Fisher, Dependence of thyroidal clearance rate on plasma iodide level. *J. Clin. Endocrinol. Metab*. **27**, 722–727 (1967).

141. H. N. Wagner, W. B. Nelp and J. H. Dowling, Use of neutron activation analysis for studying stable iodide uptake by the thyroid. *J. Clin. Invest*. **40**, 1984–1992 (1961).

142. K. F. Eckerman, R. W. Leggett, M. Cristy, C. B. Nelson, J. C. Ryman, A. L. Sjoreen and R. C. Ward, *User's Guide to the DCAL System*. ORNL/TM-2001/190, Oak Ridge National Laboratory Oak Ridge, TN, 2006.