The Biokinetic Model for Iodine

ICRP Task Group 95 Webinar

Presenting Report on Production of Dose Coefficients For the Assessment of Internal Exposure of Workers and Members of the Public

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ICRP INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION

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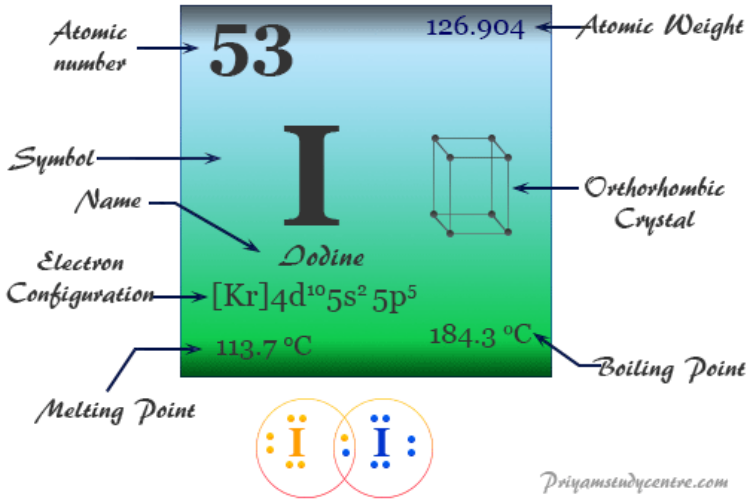
Iodine

- **Iodine is a trace element that is naturally present in the environment and some foods.**
- **Iodine is a volatile halogen that occurs mainly in oxidation states I, 0, and V.**
- **The most common chemical forms of iodine in solution are the iodide (I^-) and the iodate (IO_3^-).**
- **The body needs iodine to make thyroid hormones. These hormones control the body's metabolism and many other important functions.**

- **In industries, research and medicine iodine may be encountered in a variety of chemical and physical forms, including**
  - organic compounds
  - vapours and gases
  - particulate forms.



Isotopes of iodine

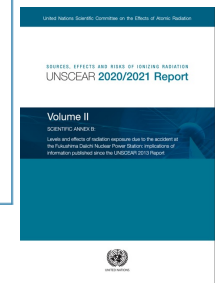
- Twenty-four isotopes of iodine, with mass numbers from 117 to 140 have been identified. All except ^{127}I are radioactive, with physical half-lives ranging from 1 s (^{140}I) to 16 × 10^6 y (^{129}I).
- Radioisotopes of iodine with mass numbers 129 and 131 through 140 are produced in fission, largely as fission fragment decay products.
- ^{131}I, ^{129}I, and ^{132}I (progeny of ^{132}Te) are the three main iodine fission products that are released from reactor accidents and are present in fragments of irradiated fuels.
- The low-mass radioisotopes of iodine (^{117}I to ^{126}I and ^{130}I) are not fission products.
- ^{123}I and ^{125}I are used in medicine as tracers for imaging and evaluating the function of the thyroid, and ^{131}I is used in medicine for the treatment of thyroid cancer.
- The heavier radioisotopes of iodine, with mass numbers 136 to 140, are produced in abundance during fission but their short physical half-lives (1.5 to 86 s) result in their decay to isotopes of xenon, cesium, barium and lanthanum in the time required for transport to and internalization by an individual.
- Iodine-127 is the end-product of a low-yield fission fragment decay chain and is stable and, therefore, radiobiologically inconsequential.

Isotope	Physical half-life	Decay mode
^{118}I	13.7 min	EC, B+
^{119}I	19.1 min	EC, B+
^{120}I	81.6 min	EC, B+
^{120m}I	53 min	EC, B+
^{121}I	2.12 h	EC, B+
^{123}I	13.27 h	EC
^{124}I	4.176 d	EC, B+
$^{125}I^*$	59.40 d	EC
^{126}I	12.93 d	EC, B+, B−
^{128}I	24.99 min	B−, EC, B+
$^{129}I^*$	1.57E+7 y	B−
^{130}I	12.36 h	B−
$^{131}I^*$	8.021 d	B−
^{132}I	2.295 h	B−
^{132m}I	1.387 h	IT, B−
^{133}I	20.8 h	B−
^{134}I	52.5 min	B−
^{135}I	6.57 h	B−

EC, electron-capture decay; B+, beta-plus decay; B−, beta-minus decay; IT, isomeric transition decay.
*Dose coefficients and bioassay data for these radionuclides are given in the printed copy of this publication. Data for other radionuclides listed in this table are given in the accompanying electronic annex.

Public exposure.
Accidents at Chornobyl and Fukushima Daiichi NPPs (UNSCEAR 2020/21)

	Chernobyl Nuclear Power Station (Unit 4)					*Fukushima Daiichi Nuclear Power Station (Units 1, 2 and 3)*				
Measurements of radioiodine in thyroid	400 000[l]					1 200				
Average individual doses to residents in different regions, municipalities or prefectures	*Group*	*Time period*	*Number (thousands)*	*Thyroid dose[m] (mGy)*	*Effective dose[m,n] (mSv)*	*Group (adults)*	*Time period*	*Number (thousands)*	*Thyroid dose[m] (mGy)*	*Effective dose[m] (mSv)*
	Evacuees	First year	115	≈500	≈50	Evacuees	First year	118	≈0.8–15	≈0.05–6
	"Contaminated areas"[o] in Belarus, Russian Federation[p] and Ukraine	First year for thyroid dose	6 400	≈100	≈13	Municipalities in Fukushima Prefecture	First year for thyroid dose	1 900	≈0.5–10	≈0.2–10
	Belarus, Russian Federation[p] and Ukraine	1986-2005 for effective dose	98 000	≈20	≈2	Municipalities in neighbouring prefectures	First ten years for effective dose	17 000	≈0.3–3	≈0.3–3
	Rest of Europe		500 000	≈1	≈0.4	Prefectures in rest of Japan		110 000	≈0.03–0.5	≈0.009–1
Ranges of individual doses	Absorbed doses to the thyroids of evacuees ranged from <50 mGy to >5 Gy, with several hundred evacuees receiving doses in excess of 5 Gy Absorbed doses to the rest of the population of Belarus, Russian Federation and Ukraine (98 million) varied over a wide range, with most receiving thyroid doses <50 mGy and about 1% doses >200 mGy					Absorbed doses to the thyroids of evacuees varied over a wide range (5th to 95th percentile) from less than about 1 mGy to about 15 mGy Absorbed doses to the thyroids of non-evacuees range up to about 15 mGy (95th percentile) with about 1% >20 mGy				

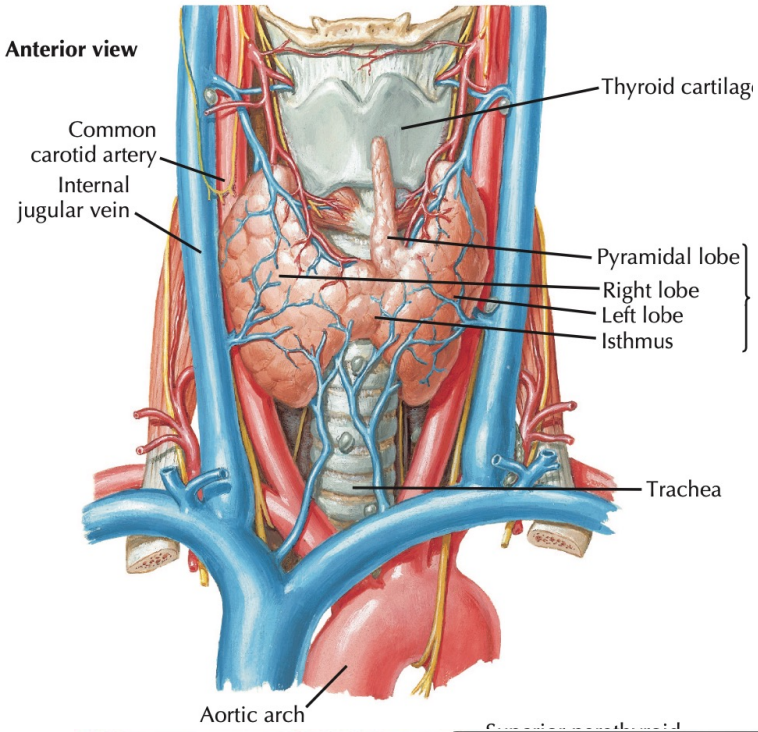


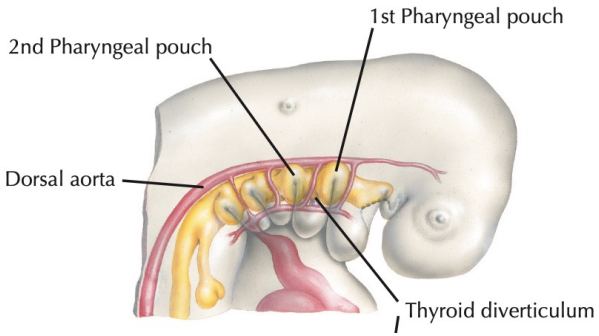
Stable iodine intake

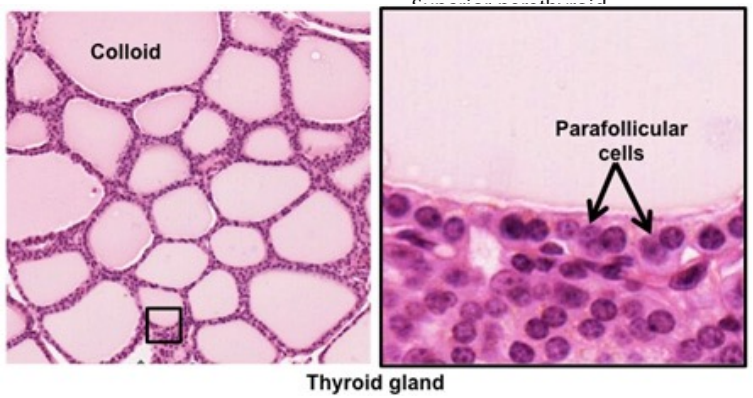
- **Ingested iodine is rapidly absorbed from the stomach and intestine and, once in the circulation, it becomes available for uptake into the thyroid gland.**
- **Iodine is largely recycled by the body after use of thyroid hormones by body tissues, but the body's supply must be supplemented with dietary iodine due to losses in excreta.**
- **The WHO recommends daily intake of 150 mg of iodine by adults, and 200 mg during pregnancy and lactation to ensure adequate production of thyroid hormones and prevention of goitre and hypothyroidism.**
- **Extensive survey data on dietary and urinary iodine indicate that iodine intake is at or above recommended levels in much of the world but is mildly to severely deficient in many regions.**
- **Daily intake of iodine is typically 30–40% lower in adult women than in men.**

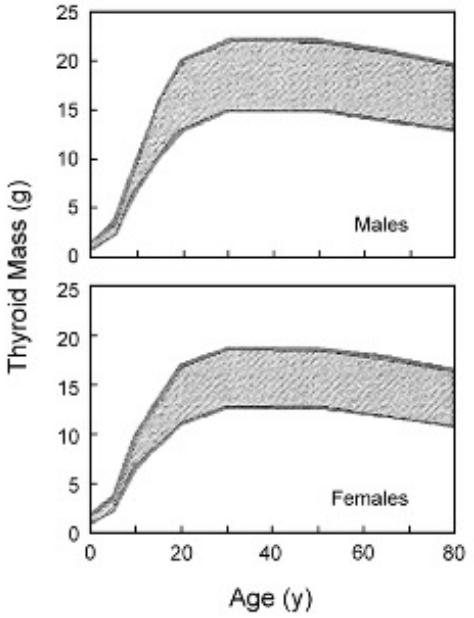
Thyroid gland

- **The thyroid gland is the earliest endocrine glandular structure to appear in fetal development. Arising from a thickening in the anterior pharyngeal floor at gestational day 16, the thyroid descends into a normal position in the base of the neck by the second month of gestation.**
- **Synthesis of thyroglobulin has been detected as early as the fifth gestational week. By week 11, the gland is often functional with thyroid hormone detectable in fetal serum.**
- **It is located in front of the neck below the thyroid cartilage and consists of two lobes.**
- **Glandular parenchyma consists of spherical follicles of various sizes (50–500 µm in diameter) whose total number may exceed 20 million.**
- **Follicle lumina are filled with gelatinous colloid made of <u>thyroglobulin</u>.**









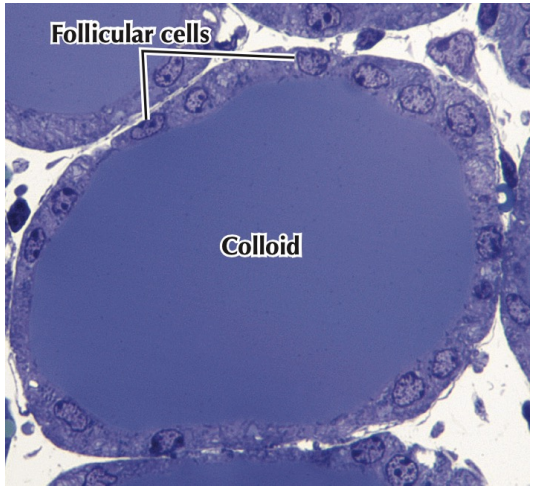
Thyroglobulin and thyroid hormones

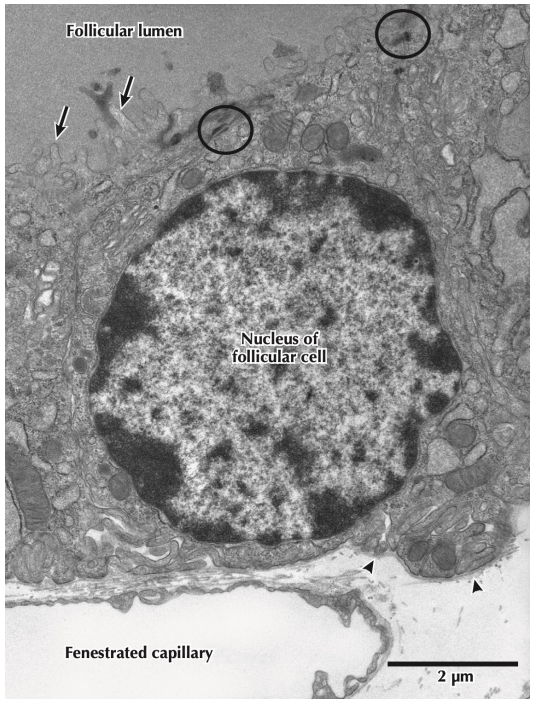
- **Thyroglobulin is iodinated glycoprotein and is the temporary storage form and precursor to main thyroid hormones**
  - triiodothyronine (**T3**)
  - tetraiodothyronine (thyroxine; **T4**).

- **Follicles are lined by simple cuboidal epithelium, which consists of thyroid follicular cells that rest on an inconspicuous basement membrane.**

- **Thyroid follicular cells are uniquely adapted to concentrate iodine and to incorporate it into thyroid hormone.**

- **Thyroid hormones**
  - increase oxygen consumption and metabolic rates of most body tissues and are essential for normal growth, maturation, and mental activity.
  - must be maintained within an optimal range for normal development and health.
  - are composed mostly of iodine (65% of T4's weight; 58% of T3's weight) which is primarily derived from the diet.





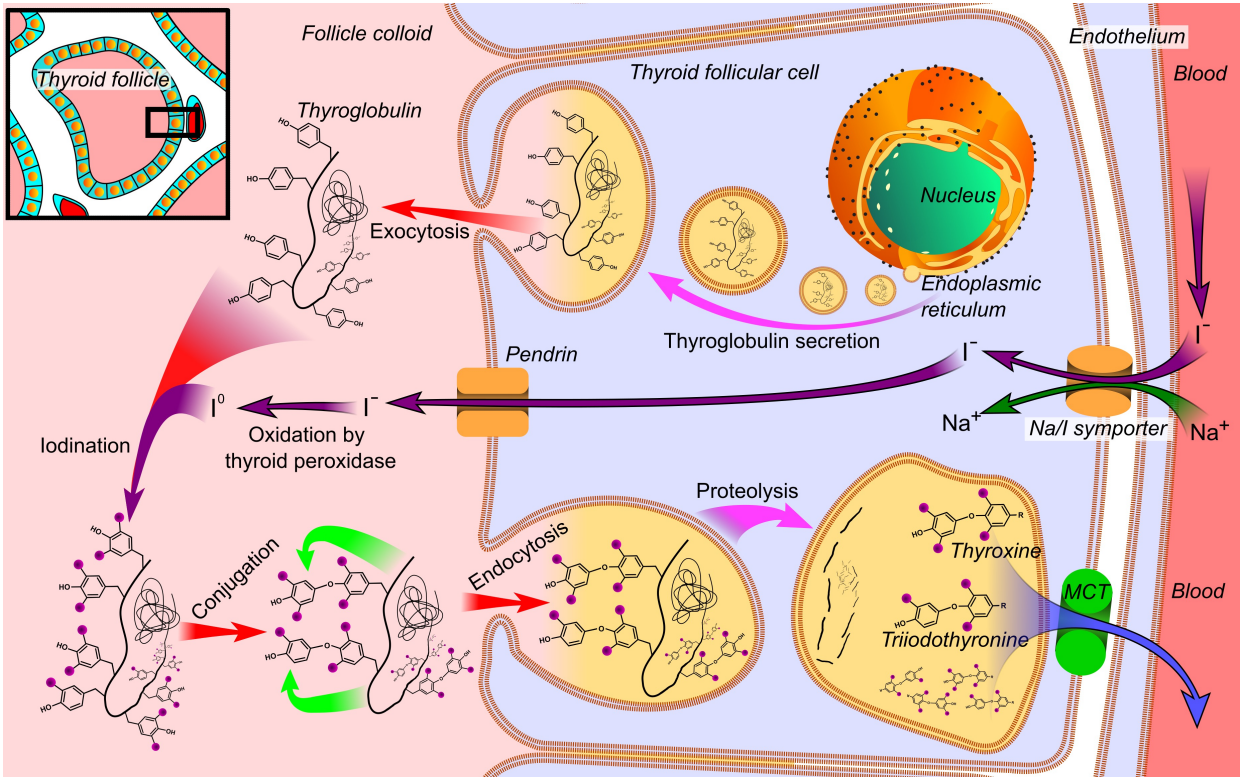
Synthesis of the thyroid hormones

- ***Thyroglobulin*** **is synthesized in the** ***endoplasmic reticulum*** **and follows the secretory pathway to enter the colloid in the lumen of the thyroid follicle by exocytosis.**

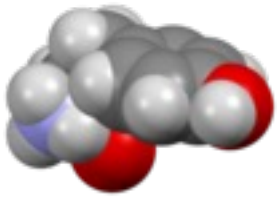
- **A** ***sodium-iodide (Na/I) symporter*** **pumps iodide (I−) actively into the cell and iodide enters the** ***follicular lumen*** **from the cytoplasm by the transporter** ***pendrin*****.**

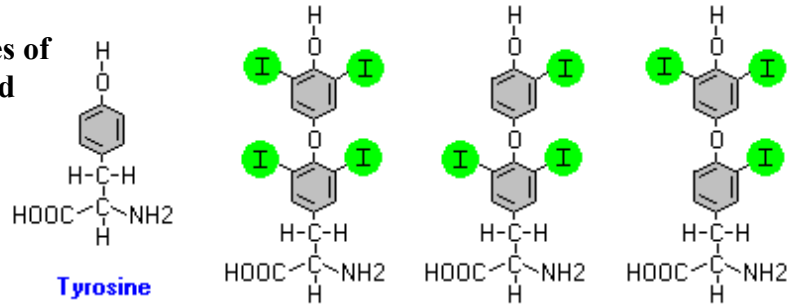
- **In the colloid, iodide (I−) is oxidized to iodine (I^0) by enzyme** ***thyroid peroxidase*****.**
- **Iodine (I^0) is very reactive and iodinates the** ***thyroglobulin*** **at** ***tyrosyl residues*** **in its protein chain, which in total containing approximately 120 tyrosyl residues.**
- **In conjugation, adjacent tyrosyl residues are paired together.**

- **Thyroglobulin re-enters the follicular cell by endocytosis.**
- **Proteolysis by various proteases liberates** ***T4*** **and** ***T3*** **molecules.**
- **Efflux of** ***T4*** **and** ***T3*** **from follicular cells, largely through** ***monocarboxylate transporter*** **(MCT) and entry into the blood.**



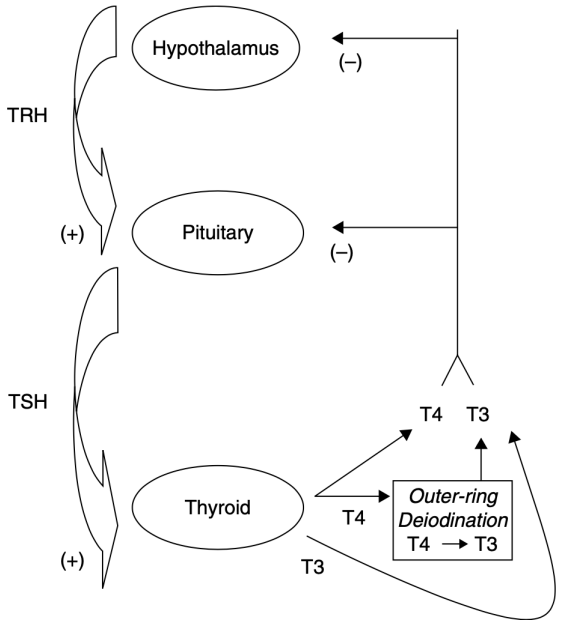
Thyroid hormones are derivatives of the the amino acid tyrosine bound covalently to iodine.

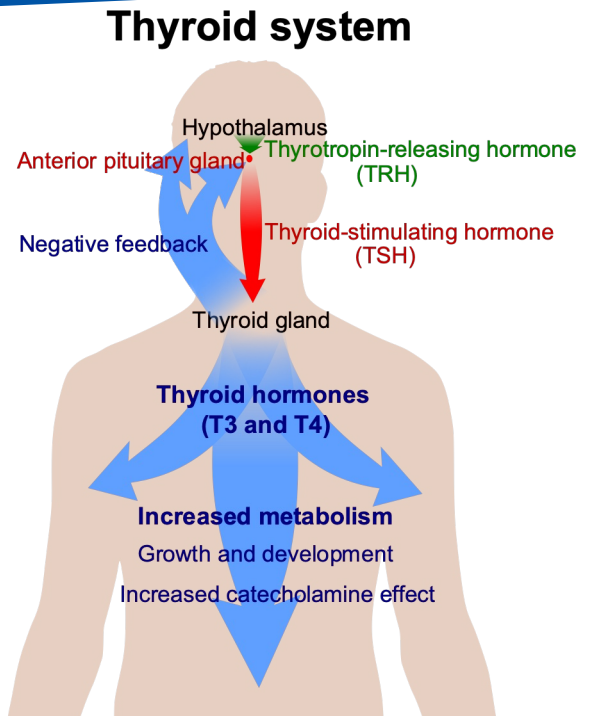




Hypothalamic-pituitary-thyroid axis

- **Thyroid hormone secretion is regulated by the *hypothalamic-pituitary-thyroid axis*.**
- **The *hypothalamus* produces thyrotropin releasing hormone (TRH), which stimulates the *pituitary* to secrete thyrotropin.**
- **Thyrotropin, also called thyroid stimulating hormone (TSH), stimulates thyroid hormone synthesis and glandular secretion.**
- **Both active thyroid hormones, T4 and T3, exert negative feedback upon the hypothalamus and the pituitary.**



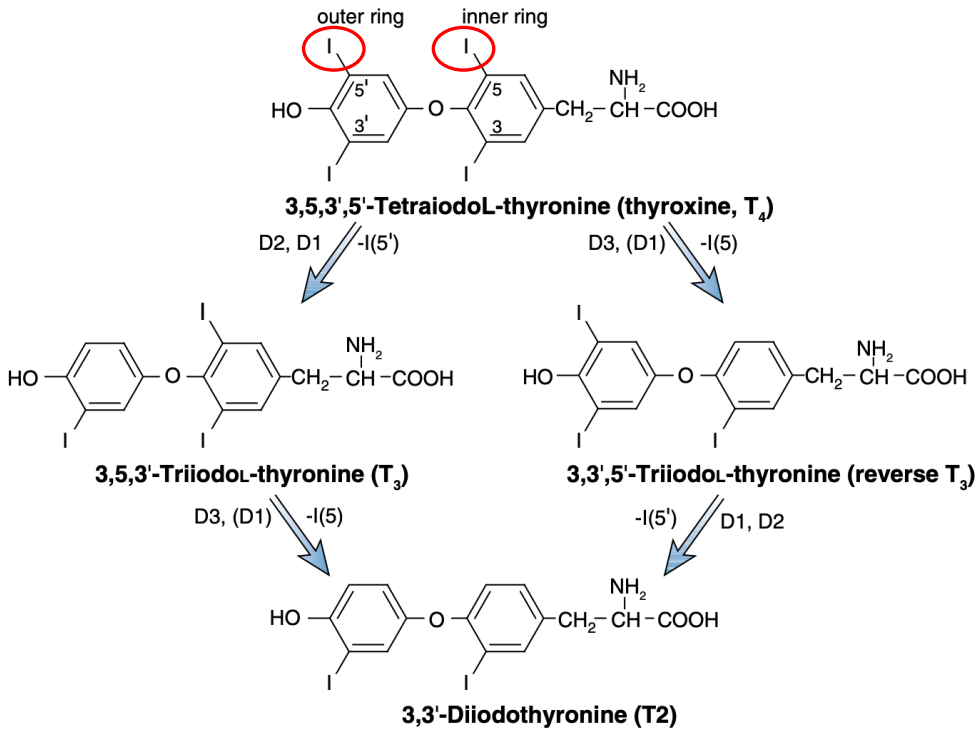


Thyroid hormone deiodination

- ***Monodeiodination*** is the major pathway of thyroid hormone metabolism in humans.
- The sequential removal of iodine atoms can lead to either substrate activation or inactivation.
- The prohormone **T4** contains four iodine atoms, two on its "outer" phenolic ring and two on its "inner" tyrosyl ring. Removal of a single iodine atom from thyroxine's **outer ring** converts it into the more biologically potent **T3**. **This reaction is catalyzed by type 1 (D1) and 2 (D2) *deiodinase enzymes*.**
- **Inner-ring** deiodination converts both T4 and T3 into **inactive metabolites**, rT3 and T2 respectively.

- While a small amount of T4 activation occurs in the thyroid gland itself, the **vast majority of T4 to T3 conversion occurs in peripheral tissues** and is catalyzed b both D1 and D2.

- **In the euthyroid state, D3-mediated inner-ring deiodination is responsible for inactivating 80% of daily thyroid hormone production**.

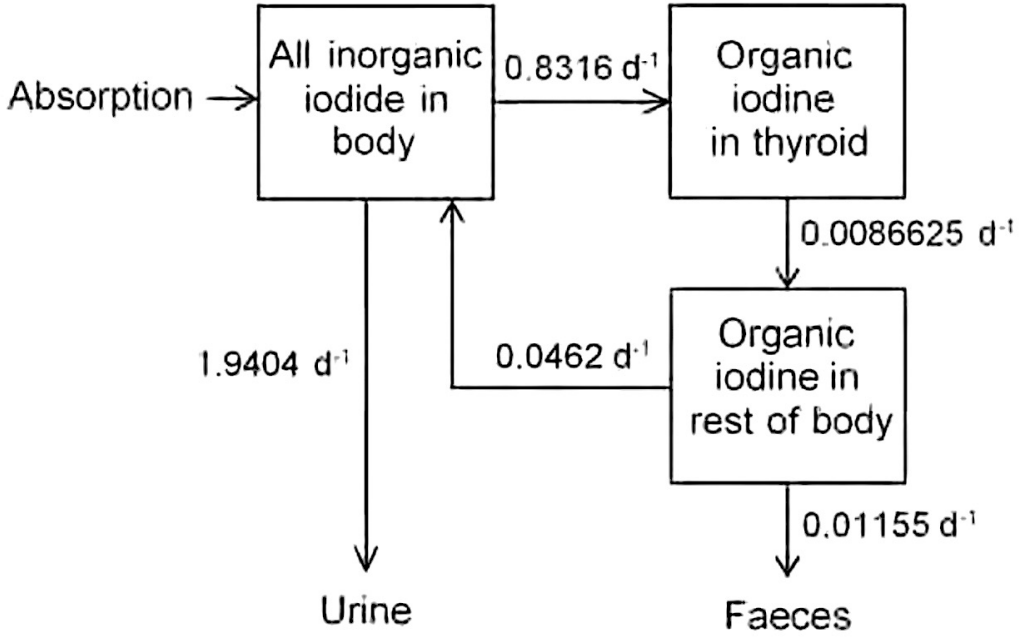


Human deiodinase enzymes

	D1	D2	D3
Enzyme activity	Outer-ring deiodination *and* inner-ring deiodination	Outer-ring deiodination	Inner-ring deiodination
Tissue expression	Liver Kidney Thyroid	Central nervous system Pituitary Brown fat Cardiac and skeletal muscle	Uterus Placenta Central nervous system Skin
Substrates	rT3, T4, T3S, T4S	T4, rT3	T3, T4
Positive regulators	Thyroid hormone	Cold exposure Bile acids Cyclic AMP Deubiquitination	Thyroid hormone Angiogenic factors TGF-β family Hypoxia Hedgehog family
Negative regulators	Cytokines Illness/fasting	Thyroid hormone Sonic hedgehog	Glucocorticoids

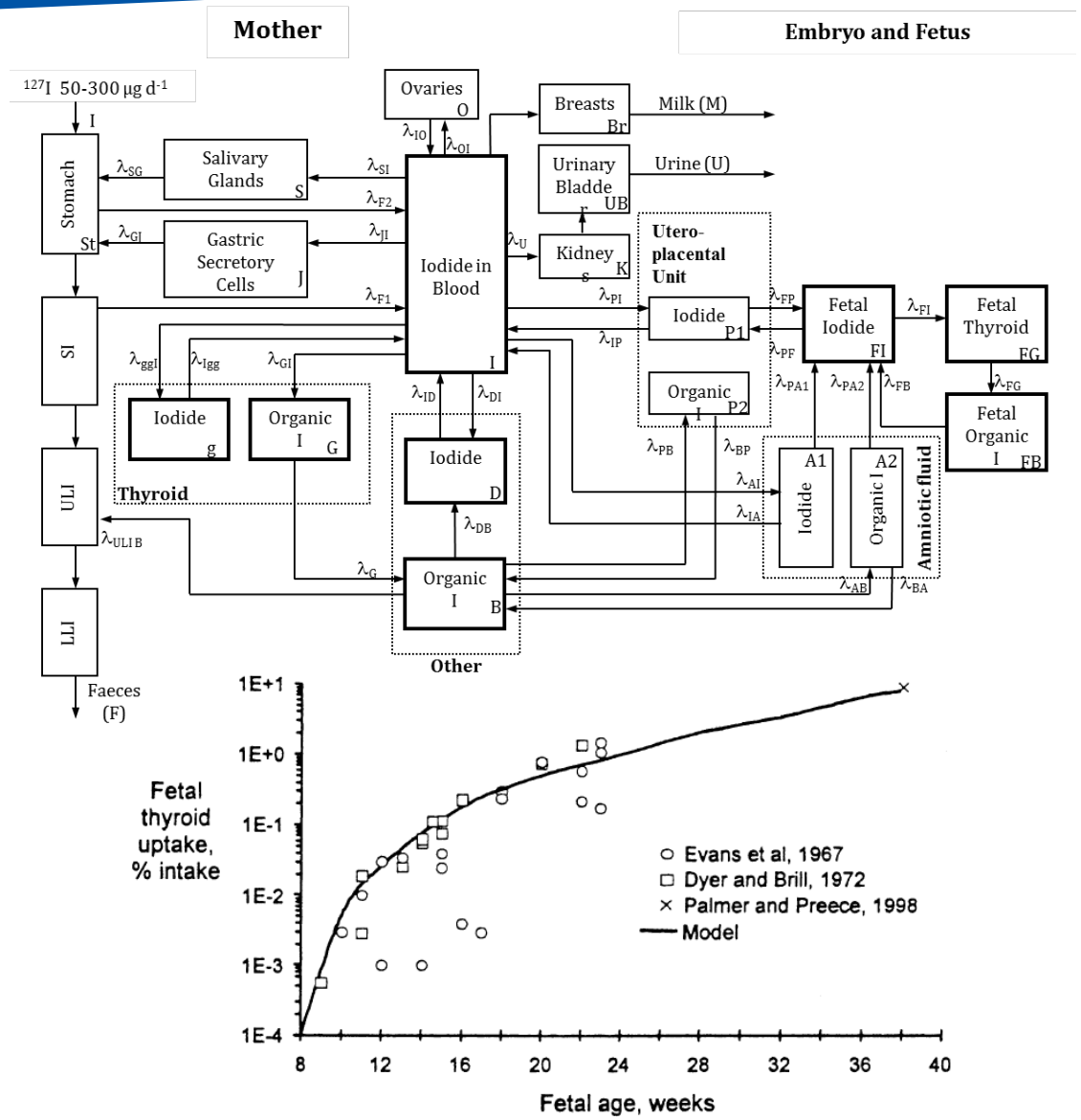
Biokinetic model introduced by Riggs (1952) and used by ICRP Publications (1994, 1997)

- One of the first “recycling” and physiologically oriented models.
- It is simple and calibrated for I-131 dosimetry.
- Not accurate for the prediction of the systemic kinetics and thyroid uptake during the day after intake.
- Underestimates thyroid doses from short-lived radioiodines, such as I-132.
- Difficult to adjust for non-reference individuals and stable iodine diet.



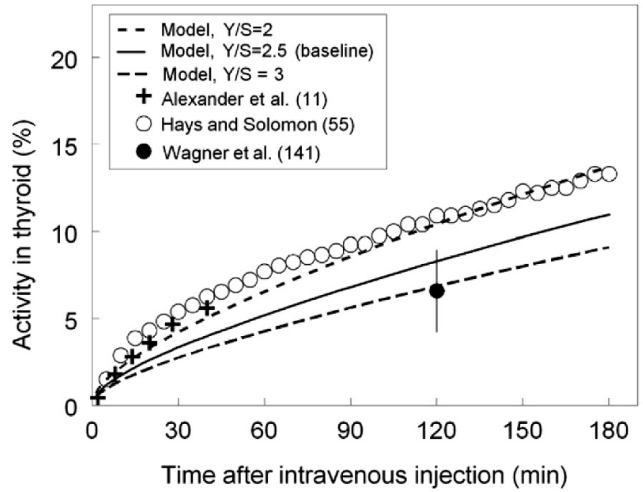
Biokinetic model for dosimetry of embryo, foetus and breastfed infants introduced by Berkovski (1999, 2002) and used in ICRP Publications 88, 95

- **Physiologically-oriented model**
- **Calibrated for:**
  - pregnancy
  - post-partum lactation.
- **Based on human and animal data**
- **Transfer coefficients are time-variable (depend on the gestation-stage).**
- **Properly model early kinetics and thyroid uptake.**
- **Adequate estimates of doses from short-lived radioiodines, such as I-132.**



Model introduced by Leggett (2010) and used in the ICRP OIR series

- **Comprehensive physiological model**
- **Describes the biokinetic of systemic iodine in terms of three subsystems:**
  - circulating (extrathyroidal) inorganic iodide;
  - thyroidal iodine (trapping and organic binding of iodide, and synthesis, storage, and secretion of thyroid hormones);
  - extrathyroidal organic iodine.
- **Properly model early kinetics and thyroid uptake**
- **Adequate estimates of doses from short-lived radioiodines, such as I-132**



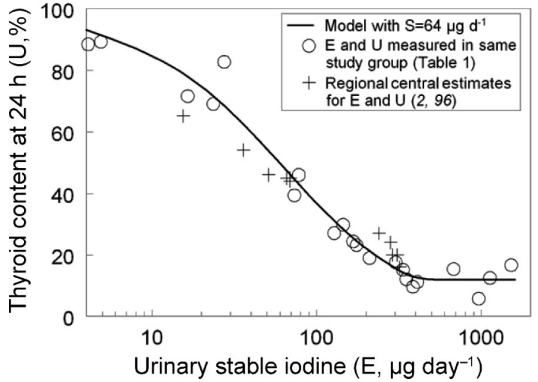
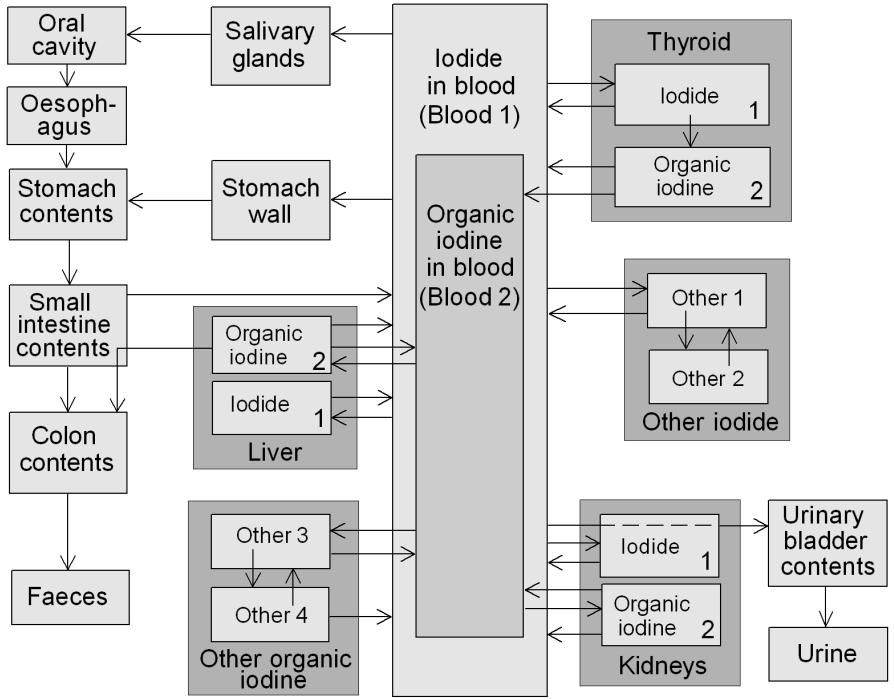


FIG. 14. Model predictions and observations of 24-h uptake of radioiodine by thyroid (U) as a function of daily urinary excretion of stable iodine (E). Values for E and U in same study group are from Table 1. Regional estimates of E and U are from refs. (*2, 96*).



Quantity	Dietary iodine (μg day⁻¹)/thyroidal secretion of organic iodine (μg day⁻¹) 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).

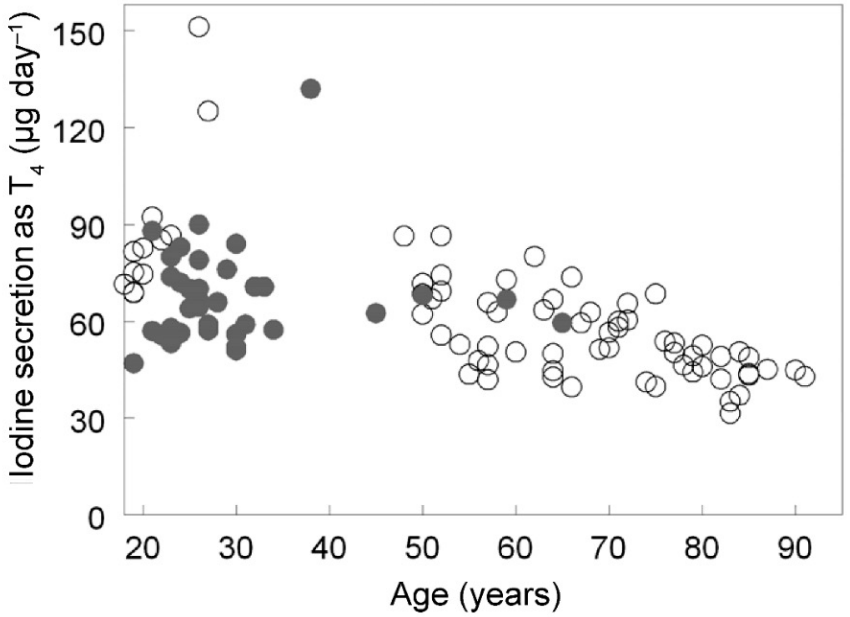
Examples of clinical data used in new model

Relationship of 24-h Uptake of Ingested Radioiodine by Thyroid (U) and Average Daily Urinary Excretion of Stable Iodine (E), Adult Subjects

Study	No. of subjects[a]	Observed values[b] E (μg day^{-1})	Observed values[b] 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).

Rate of secretion of hormonal iodine as T4 in adult male humans. Data from various sources



Baseline parameter values

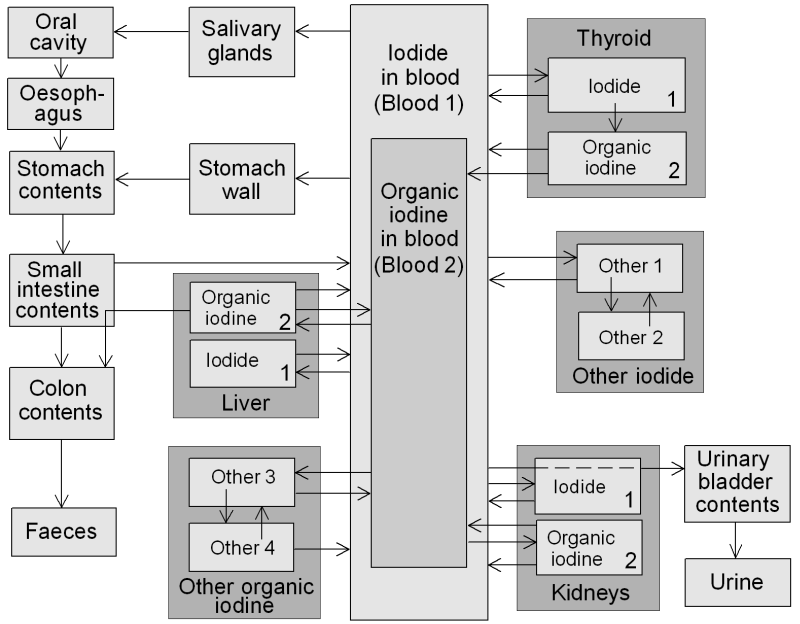
Pathway	Transfer coefficient (d^{-1})
Blood 1 to Thyroid 1	7.26*
Blood 1 to urinary bladder contents	11.84
Blood 1 to salivary gland	5.16
Blood 1 to stomach wall	8.60
Blood 1 to Other 1†	600
Blood 1 to Kidneys 1	25
Blood 1 to Liver 1	15
Salivary gland to oral cavity	50
Stomach wall to stomach contents	50
Thyroid 1 to Thyroid 2	95
Thyroid 1 to Blood 1	36
Thyroid 2 to Blood 2‡	0.0077
Thyroid 2 to Blood 1	0§
Other 1 to Blood 1	330
Other 1 to Other 2†	35
Other 2 to Other 1	56

Pathway	Transfer coefficient (d^{-1})
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

*Depends on the Y:S ratio, where Y (μg d^{-1}) is dietary intake of stable iodine and S (μg d^{-1}) is the rate of secretion of hormonal stable iodine by the thyroid.
†For dosimetric purposes, each of the compartments Other 1, Other 2, Other 3, and Other 4 are assumed to be uniformly distributed in all remaining (not explicitly identified) tissues.
‡For high intake of stable iodine, the outflow from Thyroid 2 is split between Blood 2 and Blood 1 as described by Leggett (2010).
§Non-zero only for high intake of stable iodine (Leggett, 2010).

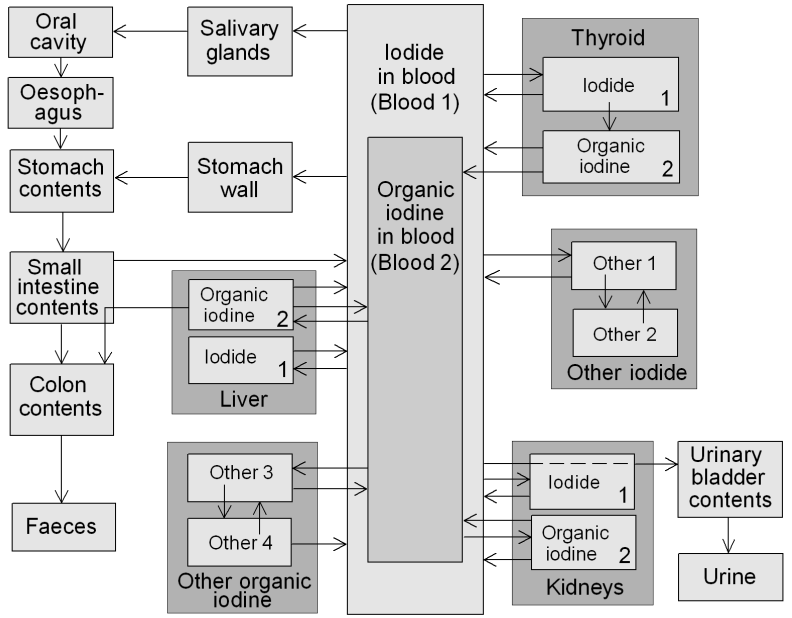
Extrathyroidal inorganic iodide

- **The modelled behaviour of extrathyroidal inorganic iodide is based on bioassay clinical data on ^{131}I in young adult males during the first 3 h after intravenous injection. The following compartments are used:**
  - a compartment representing iodide in blood plasma plus red blood cells, treated as a well-mixed pool (Blood 1);
  - salivary glands;
  - stomach wall;
  - Liver 1, representing iodide in liver; Kidneys 1, representing iodide in kidneys;
  - Other 1, representing rapidly exchangeable iodide in extracellular fluids of extrathyroidal tissues other than kidneys and liver;
  - Other 2, representing slowly exchangeable iodide in extrathyroidal tissues other than kidneys and liver; and
  - a series of compartments representing different segments of the alimentary tract as represented in the HATM.



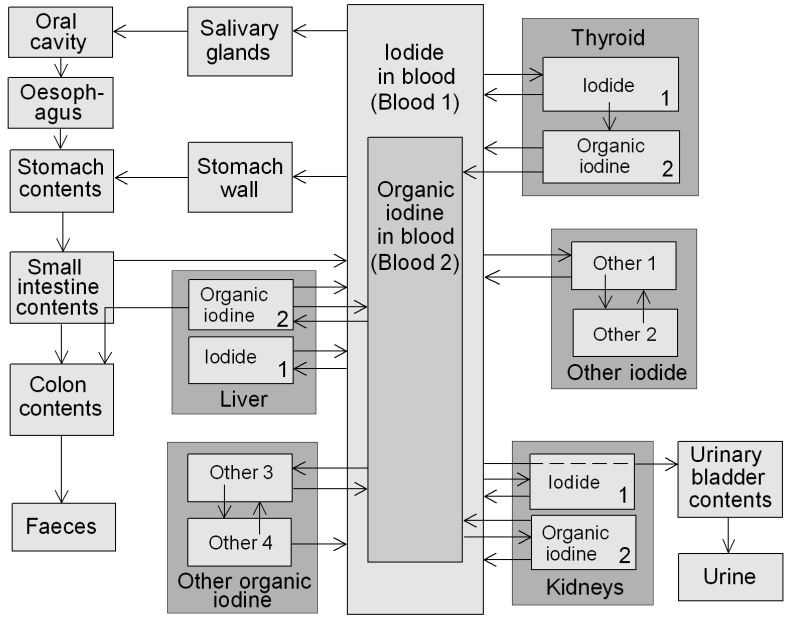
Iodine in the thyroid

- **The behaviour of iodine in the thyroid is described in terms of two compartments representing:**
  - inorganic iodide (Thyroid 1)
  - organic iodine (Thyroid 2).
- **Thyroid 1 receives iodide from Blood 1, feeds iodide to Thyroid 2, and leaks some iodide back to Blood 1.**
- **Thyroid 2 converts iodide to organic iodine and transfers organic iodine into the blood organic iodine pool (Blood 2).**
- **An arrow representing leakage of activity from Thyroid 2 into Blood 1 is included for application of the model to subject with unusually high dietary iodine, but the baseline transfer coefficient from Thyroid 2 to Blood 1 is set to zero.**

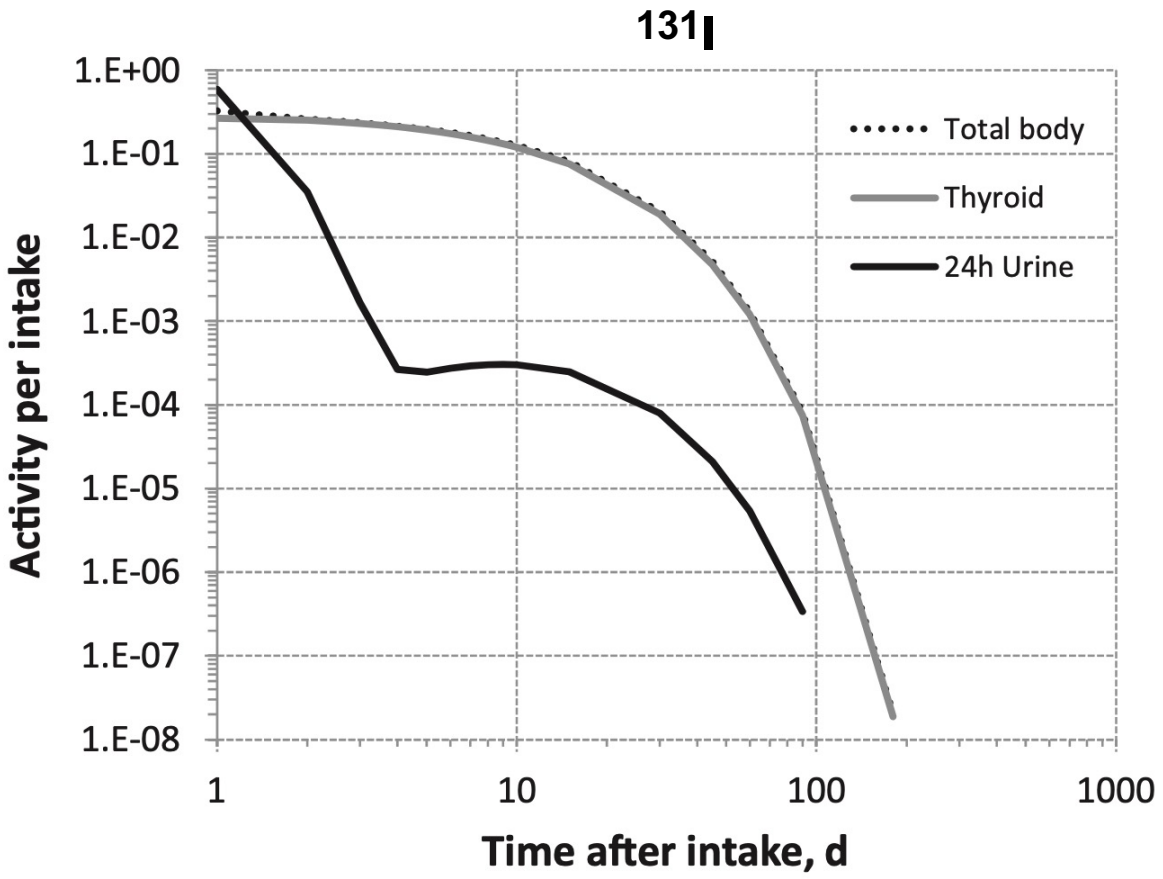


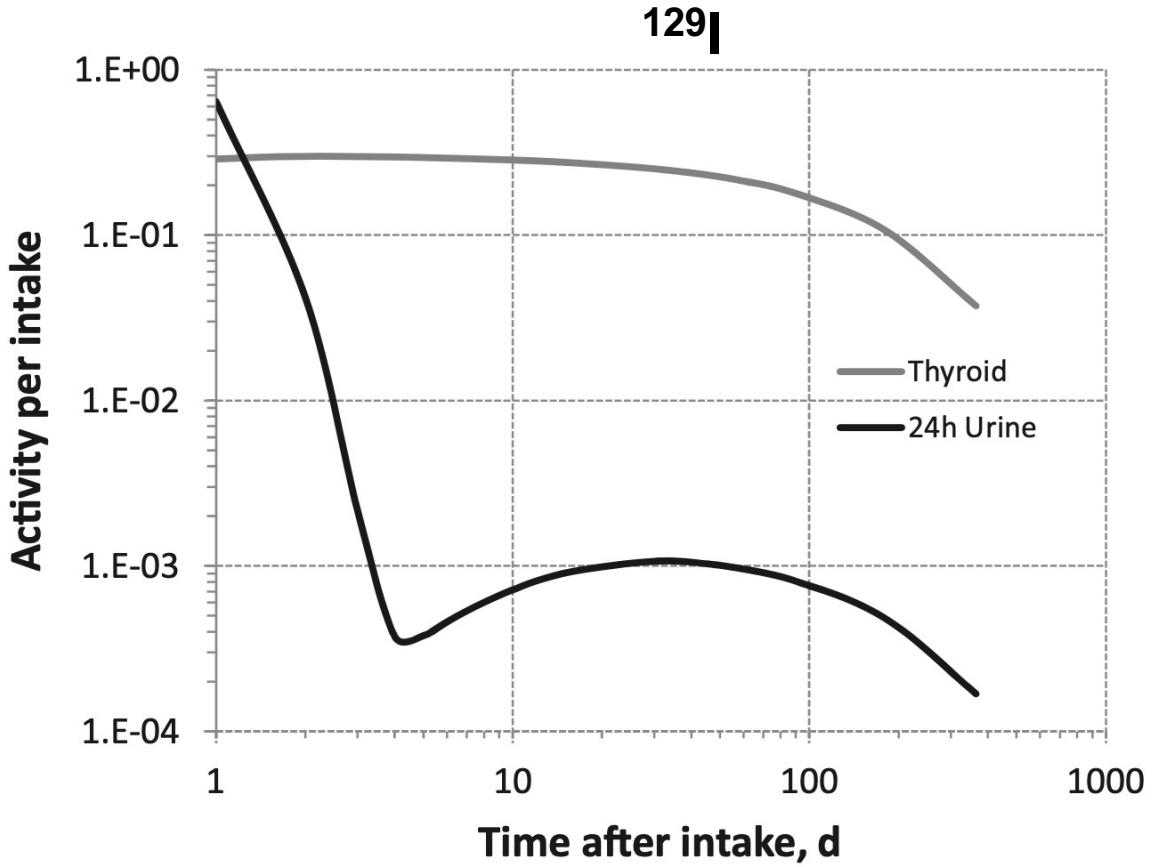
Extrathyroidal organic iodine

- **The modelled behaviour of extrathyroidal organic iodine is an extension of a model of extrathyroidal T4 kinetics developed by Nicoloff and Dowling (1968) from measurements of ^{131}I-labelled T4 in 13 healthy human subjects (seven women and six men).**
- **The present model adds a compartment representing organic iodine in the kidneys, and assumed to have the same rate of exchange with blood plasma per gram of tissue as does the liver.**
- **The following compartments are used to describe the behaviour of extrathyroidal organic iodine:**
  - Blood 2, representing thyroid hormones bound to plasma proteins;
  - Liver 2, representing organic iodine in liver;
  - Kidneys 2, representing organic iodine in kidneys;
  - Other 3, representing rapidly exchangeable organic iodine in extracellular fluids of extrathyroidal tissues other than kidneys and liver; and
  - Other 4, representing slowly exchangeable organic iodine in extrathyroidal tissues other than kidneys and liver.



Thyroid content and daily urinary excretion following inhalation of 1 Bq elemental iodine





Comparison of Absorbed Dose per Unit Intake of Radioiodine by an Adult Male Based on the ICRP OIR Model and the previous ICRP Model (Leggett, 2010)

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

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