Evaluation of Implementation Strategies for Potassium Iodide: Iodide Biokinetic and Physiological System Modeling

Literature Review

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1.1 Overview of Thyroid Function

The thyroid is a butterfly-shaped gland located under the skin at the front of the neck. It is a part of the endocrine system and controls many important functions by producing and secreting hormones. The thyroid is responsible for the formation and secretion of thyroid hormones as well as iodine homeostasis within the human body. The thyroid produces approximately 90 percent of inactive thyroid hormone, or thyroxine (T4), and 10 percent of active thyroid hormone, or triiodothyronine (T3). These hormones are important for metabolism, energy production, body temperature, heart rate, bone growth, reproductive function, and other bodily functions.

1.2 Iodine Biokinetics

Iodine is involved in carrying out several biological functions. Iodine is used in the thyroid to synthesize the T4 and T3 hormones. Immediately after ingestion, iodine enters the bloodstream primarily through absorption in the small intestine. Absorption of iodine can be delayed for up to 3 hours if it is ingested with food [Ref. 1]. Iodine is swallowed when inhaled, absorbed by the digestive system, and enters the bloodstream within several seconds to 10 minutes, depending on the physical state of the iodine. The iodine in the bloodstream is distributed quickly throughout the extracellular fluids. Most of the iodide that enters the is extracellular fluids returned to the bloodstream within an hour [Ref. 2]. An equilibrium between the blood and the extracellular fluids occurs within several minutes.

The thyroid and the kidney compete for the iodine in the body. The kidney filters iodine out of the bloodstream and excretes it as urine after entering the urinary bladder. Most iodine is removed from the body due to the renal clearance. Small amounts of iodine are removed by sweat, saliva, tears, and bile.

Iodine is taken up into the thyroid by active transport from the bloodstream by the Sodium-Iodide Symporter (NIS) channel. The NIS channel can be saturated if an acute intake of iodine is absorbed [Ref. 3]. The iodine is taken up in the thyroid by thyroid-stimulating hormones and used to create T4 and T3, which are then released back into the bloodstream [Ref. 4]. Clearance of iodine in the thyroid depends on the volume and activity of the gland. The dietary iodine intake and blood iodine concentration drives the thyroids clearance process [Ref. 5].

Thyroid clearance of iodine significantly increases between birth and approximately 6 years of age. In adolescents, the clearance slightly increases compared to adults and progressively decreases with age [Refs 6 and 7]. There appears to be little change to the uptake of iodine in the thyroid except for the first two weeks after birth when a substantial increase is observed compared to adults [Ref. 7]. A fetus begins taking up iodine at about 12 weeks. After 22 weeks gestation, the uptake begins to rapidly increase until full-term. Unlike other adults, pregnant women show increased thyroid uptake of iodide, especially during the first trimester. As pregnancy advances, fetal iodine uptake rises significantly during the second and third

trimesters. Since both stable and radioactive iodine can cross the placenta, fetuses are vulnerable to radioactive iodine exposure [Ref. 8]. The fetus has a much smaller body size and thyroid gland, with an iodine pool that is only a fraction of the mothers. The fetus' smaller iodine pool leads to more concentrated accumulation within the fetal thyroid when iodine is taken up. The mother's larger iodine pool dilutes any incoming iodine, meaning a smaller fraction of the total ends up in her thyroid. Iodine taken up by the fetus becomes concentrated in the small fetal thyroid, leading to a higher local concentration compared to the maternal thyroid.

1.3 Thyroid Blocking Mechanism

When an acute dose of iodine is taken up, a mechanism called the Wollf-Chaikoff effect begins to take place. Temporarily, the thyroid hormone production is suspended through synthesis of inhibitors to the production of hydrogen peroxide, which is required for thyroid hormone synthesis. The inhibition process take place within hours of the acute intake of iodine. As the concentration of iodine in the thyroid is lowered, the effect is slowed, and function continues [Ref. 9]. The production of thyroid hormones resumes within 24 to 48 hours following an acute intake of iodine. The thyroid also has a mechanism to escape the blocking effect in cases of prolonged high iodine intake by downregulating the expression of the NIS [Ref. 10]. This mechanism makes it possible to tolerate sustained large doses of iodine with little clinical effects [Ref. 11]. A fetus is sensitive to the Wolff-Chaikoff effect due to a low thyroid iodine pool and a high requirement for iodine. Also, the ability to escape the effect does not appear until about 36 weeks of gestation [Ref. 12].

2.0 THYROID IODINE BLOCKING IN A NUCLEAR POWER PLANT ACCIDENT

Radioactive iodine is a nuclear fission product, and significant quantities of radioiodine could be released in very severe nuclear power plant (NPP) accidents. A few days to several weeks after a nuclear incident, iodine-131 (I-131) is the dominant contributor to internal dose. The shorter-lived iodine isotopes (i.e., I-132, I-133, I-134, and I-135) may comprise a large quantity of radioactive iodine during the early hours and days after a nuclear incident [Ref. 7]. Radioactive iodine cannot be distinguished from stable iodine when ingested or inhaled. Therefore, just like stable iodine, radioactive iodine is taken up into the thyroid leading to the thyroid receiving large doses of radiation.

After an acute dose of radioactive iodine, children and adolescents have been found to be at higher risk for developing thyroid diseases compared to adults, due to their smaller thyroid gland. The thyroid development during childhood and adolescence leads to a five to ten-fold increase of committed radiation dose, higher uptake of radioactive iodine, and higher sensitivity to radioactive iodine release of the organs, tissues and cells [Ref. 13]. Exposure to I-131 in childhood increases the risk of thyroid cancer, with both iodine deficiency and supplementation influencing this risk [Ref. 14].

Additionally, in lactating females, radioactive iodine is concentrated in the maternal milk. This is a major pathway for excretion within the 48 hours after ingestion of iodine for lactating female [Ref. 12]. Ingestion of the maternal milk after a nuclear accident would lead to an increased dose to the thyroid. Higher amounts of I-131 can be transferred to infants through breastfeeding than to the fetus during pregnancy. To reduce the risk of hypothyroidism during the crucial period of neonatal brain development, repeated administration of potassium iodide (KI) should be avoided [Ref. 8]. Likewise, repeated KI dosing in pregnant women should be avoided, as excess stable iodine can suppress fetal thyroid function and negatively affect cognitive development.

Proper thyroid function is essential for healthy fetal brain development. Both fetuses and newborns are not only sensitive to absorbing radioiodine but are also at risk of developing hypothyroidism from repeated KI administration [Ref. 8]. As a result, neonates who receive KI in the first weeks after birth should be closely monitored for changes in thyroid-stimulating hormones with thyroid hormone therapy initiated if hypothyroidism is detected. Likewise, if a breastfeeding mother requires multiple KI doses, her infant should also be monitored for signs of hypothyroidism and treated as necessary.

During a NPP accident, a protective action that could trigger the Wolff-Chaikoff effect and limit the uptake of radioactive iodine is oral administration of KI see Figure 1 [Ref. 11]. KI can diminish the radioactive iodine effective half-life by preventing its recycling in the thyroid. Depending on the initial dose of KI, the thyroid can block radioactive iodine uptake for 48-72 hours. Continuous radioactive iodine blocking could be maintained with repeated uptake of KI after initial administration [Ref. 12]. The administration of KI before or at the start of nuclear accident will lower the estimated radiation dose to the thyroid.

The timing of the administration of KI is critical in determining the efficacy of radioactive iodine blockage. It is recommended that KI administration occurs prior to 24 hours and up to several hours after the radioactive iodine exposure. The intake of KI within two hours after exposure to radioactive iodine release has been simulated to result in a blocking effectiveness of 80 percent [Ref. 15]. KI blocking capacity decreases with increased time after administration. In practical situations, optimal timing in the administration of KI is nearly impossible due to the unexcepted changes of the environmental release and dispersion of radioactive iodine.

In rare situations of unavoidable ingestion of contaminated food and drink, repeated administration of KI should be considered [Ref. 11]. Also, interdiction of contaminated food can be effective in preventing ingestion. In Poland, administration of KI and restrictions on contaminated food reduced the thyroid dose up to 70 percent [Ref. 16].

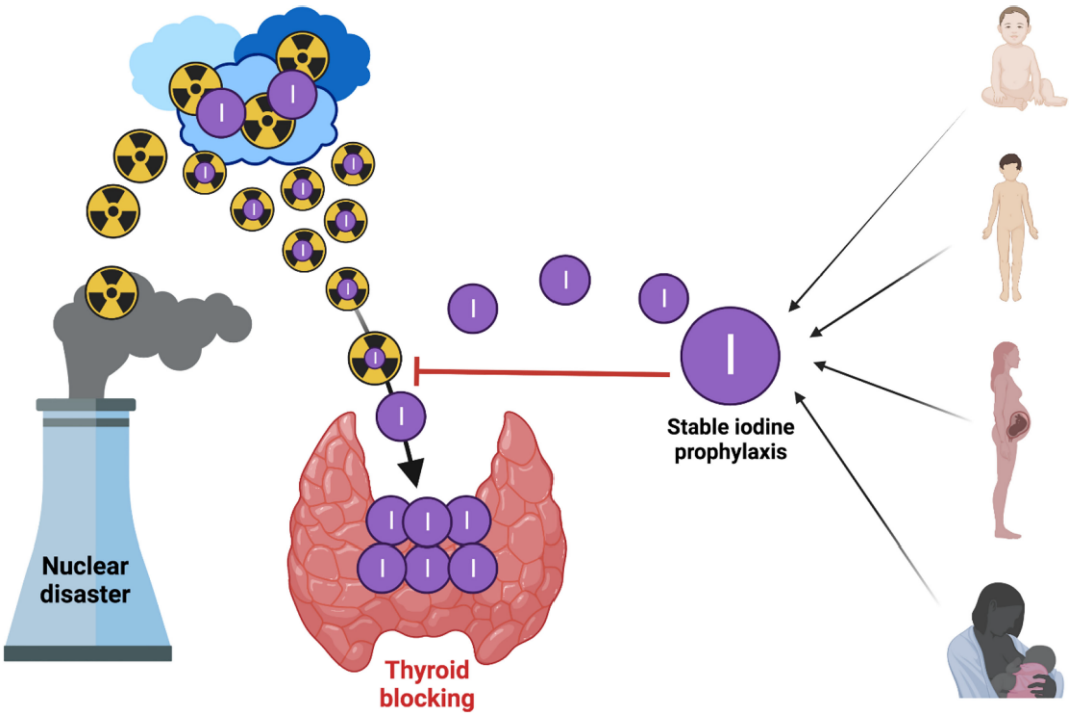

Figure 1 Blocking the Thyroid with Oral Administration of KI to Prevent Uptake of Radioactive Iodine Isotopes

3.0 ADVERSE EFFECTS OF POTASSIUM IODIDE LITERATURE REVIEW

3.1 Spallek (2011)

The studies identified in this report did not reveal severe adverse reactions to KI in the public. Scientifically sound studies on adverse effects are weak and limited due to the amount of systematic information on adverse effects of iodine thyroid blocking and most of the data being only indirectly relevant [Ref. 17]. This report states that persons with known iodine sensitivity, such as newborns and elderly people, might be at a higher risk of developing adverse effects. Indeed, the elevated iodine necessities relative to body weight, lower reserves of intrathyroidal iodine in newborns and the higher prevalence of thyroid dysfunction and other comorbidities in the elderly may predispose to adverse reactions in both groups. Due to limited available data, a dose-response relationship between KI and adverse effects could not be established; however, the risk of adverse effects can be strongly influenced by the population's nutritional iodine status.

3.2 Nauman (1993)

A survey of the Polish population was completed after the Chernobyl NPP accident. Few adverse effects were reported on the over 34,000 participants in a subsequent population-based survey. No permanent effects to thyroid function were detected between children that received KI versus children who did not receive KI. Of the newborns that received KI between three and five days after birth, a transient thyroid-stimulating hormone increase was observed in 0.37 percent newborns. No significant differences between the thyroid status of children born in 1986 and examined in the second and third year after birth compared with that in an age and sex matched group born in 1987. Only 0.2 percent of the population studied were estimated to have medically significant extrathyroidal adverse effects (e.g., headache, abdominal pain, diarrhea, vomiting, dyspnea, and eczema) to KI.

3.3 Pfinder (2016)

This report was a systematic review of the effects of KI administration in the case of accidental radioactive iodine release on thyroid cancer, hypothyroidism and benign thyroid nodules. Four studies were included in this review. Of the four included studies, two studies are case-control studies [Refs. 14 and 18], one study is an analytic cohort [Ref. 19], and one is a cross-sectional study [Ref. 20]. The authors identified low to very low quality of evidence that KI administration after a NPP accident resulted in a reduction of risk of thyroid cancer in children. The key methodological limitations were not controlling for confounding variables and poor study design. Limitations in the study design execution, as well as imprecision in the survey methods were major weaknesses for the outcomes. Across the studies, the timing and the quantity of KI intake was not specified, and therefore, the results may be biased in unknown ways. No conclusions can be drawn about the effectiveness of KI intake to prevent hypothyroidism and benign thyroid nodules due to a lack of information.

3.4 de Silva Lopes (2024)

This report is a focus review that highlights adverse effects of KI. The report states that systematic evaluations of KI adverse effects are limited, with existing studies often relying on low evidence designs. Most research focuses on radiation exposure rather than the specific side effects of KI, partly due to its unsystematic administration in exposed populations. Adverse effects are rare when KI is given at low doses for short periods (less than two weeks), with common side effects including gastrointestinal issues like nausea, vomiting, diarrhea, and stomach pain. High doses of KI (≥65 milligrams) or prolonged use can lead to iodine poisoning (iodism), characterized by headaches, gum soreness, blurred vision, and excessive nasal or eye secretions. KI may also cause iododerma, a rare skin condition marked by severe acne-like or urticarial lesions. Other systemic effects include urticaria, fever, eosinophilia, jaundice, pruritus, angioedema, and bronchospasm. High iodine doses administered through this medication can affect thyroid metabolism, potentially triggering the Wolff–Chaikoff effect and causing hypothyroidism. Although autoregulatory mechanisms typically help maintain normal thyroid function in euthyroid individuals, disruptions in these mechanisms can lead to hormonal imbalances. If thyroid autoregulation is impaired or absent, the Wolff–Chaikoff effect is more likely to occur, resulting in elevated thyroid-stimulating hormones levels and the subsequent onset of hypothyroidism and goiter.

4.0 THE PHYSIOLOGICAL SYSTEM MODEL FOR IODINE

4.1 Legget (2010)

The International Commission on Radiological Protection (ICRP) originally used a three-compartment model as a biokinetic model for intake of radioactive iodine Refs. 21 and 22]. The ICRP Occupational Intakes of Radionuclides Series adopted a new model that has more compartments, and which has remarkably increased specificity and subdivision in the iodine compartments (Figure 2) [Ref. 23].

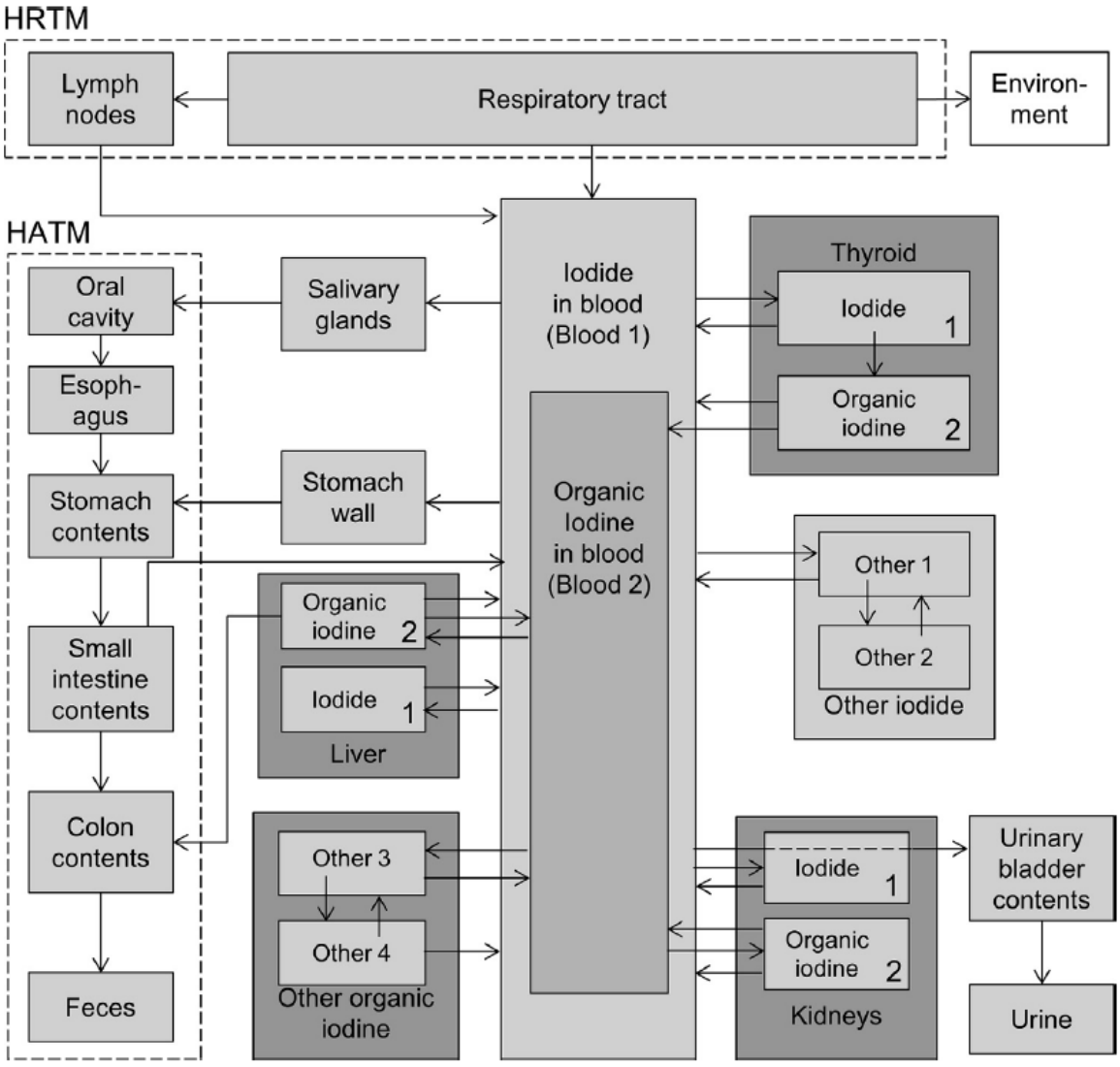

Figure 2 New ICRP Biokinetic Model for Iodine with the Human Alimentary Tract Model and the Human Respiratory Tract Model

The updated biokinetic model for iodine consolidates and extends existing physiological system models describing three subsystems of the iodine cycle in the human body: (1) circulating inorganic iodine, (2) thyroidal iodine, and (3) extrathyroidal organic iodine. Extrathyroidal iodine, which was integrated as a single compartment in the three-compartment model, was divided into specific organ compartments: blood, salivary glands, liver, kidneys, and other iodine compartments. Separation of the blood compartment from these organ compartments allows the blood iodine content to be calculated directly and more accurately.

In addition, inorganic iodine and organic iodine compartments were chemically separated in the model, and thus single organs were physically subdivided into inorganic and organic compartments. This chemical state specification facilitated a more detailed description of iodine behavior and iodine biokinetics within the thyroid. In the updated model, the uptake into the thyroid and subsequent binding can be mathematically distinguished; unbound inorganic iodine can return to the blood without long retention, and organically bound iodine is also allowed to leak into the inorganic blood compartment in cases of high dietary levels.

The thyroid blocking mechanism is now represented by inhibiting the thyroid from creating T4 and T3. The acute intake of KI leads to near complete inhibition of hydrogen peroxide generation, which is required for thyroid hormone synthesis. The aims for updating the biokinetic model for iodine was to account for the influence of dietary stable iodine, improve the radiation dose estimate for short-lived isotopes of iodine, and provide a model of the thyroid intended for dosimetry of radioiodine during thyroid blocking.

In Legget (2010), the dose coefficients for the selected iodine isotopes based on the current ICRP iodine biokinetic model were compared with values based the models and methods of ICRP Publication 68 see Table 1 [Ref. 21]. Interestingly, the current ICRP model yields similar estimates of absorbed dose to the thyroid for isotopes with half-life greater than a few hours (including I-131). Generally, the updated model shows higher dose per unit intake for iodine isotopes with short lived half-life. The difference in the dose coefficients for the thyroid is due to more detailed tracking of iodine and the difference in the representations of the thyroid blocking mechanism. The dose coefficients for I-131 and other isotopes of radioactive iodine can be found in ICRP Publication 137 [Ref. 24].

Table 1 Comparison of Absorbed Dose per Unit Intake of Radioactive Iodine by an Adult Male Based on the Current Model and ICRP 68 Systemic Model for Workers

		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

4.2 Legget (2017)

As described in this report, the factors that have compelling evidence for age dependence are elevated thyroidal uptake of iodine in the first week or two of after birth, the biological half-life of organic iodine in the thyroid, and the biological half-time of extrathyroidal organic iodine. The non-systemic features (i.e., those describing movement through the alimentary tract or removal via the urinary bladder) of the biokinetic model for iodine also show differences with age but are not described in depth in this report. Thyroid function during the first weeks of life is considered hyperactivity. At 8 to 12 weeks of age, the elevated iodine uptake returns to normal childhood levels. Outside of this hyperactivity period in early infancy, there seem to be little variance of iodine uptake until the fifth or sixth decade of life where a modest decline is observed. Little if any change in biological half-life occurs from early adulthood until middle age, after which there may be a moderate decline. Biological half-life of iodine in the thyroid largely increases between birth and about 6 years of age, followed by a more moderate increase until early adulthood.

Table 2 compares the ratios of the cumulative activities (A:B) predicted by the model reference in this paper and the ICRP Publication 56 model (B) [Ref. 26]. The proposed model projected significantly greater cumulative activity in the thyroid for radioiodine with a half-life of up to a few hours, while showing only a slight variation for longer-lived iodine isotopes. For cases of acute I-131 intake into the bloodstream in individuals with a blocked thyroid, Table 3 presents a comparison of thyroid activity. According to the proposed model, the cumulative activity in the

thyroid accounts for approximately 5 percent of the nuclear transformations in the body, whereas the ICRP Publication 56 model predicts no cumulative activity in the thyroid. In this scenario, the effective dose would primarily be influenced by non-thyroidal tissues, regardless of the biokinetic model applied.

Table 2 Comparison of Predicted Cumulative Activity of Radioiodine in the Thyroid Based on the Current Model and the ICRP's Current Age-Specific Model for Iodine

Isotope (half-life)	Ratio of cumulative activity, This model : Pub. 56, for indicated age at intake					
	100 d	1 y	5 y	10 y	15 y	Adult
I-118 (13.7 m)	2.2	2.2	2.2	2.2	2.2	2.2
I-118m (8.5 m)	2.6	2.6	2.6	2.6	2.6	2.6
I-119 (19.1 m)	1.9	1.9	1.9	1.9	1.9	1.9
I-120 (81.6 m)	1.3	1.3	1.3	1.3	1.3	1.3
I-120m (53 m)	1.5	1.5	1.5	1.5	1.5	1.5
I-121 (2.12 h)	1.3	1.3	1.3	1.3	1.3	1.3
I-122 (3.63 m)	3.5	3.5	3.5	3.5	3.5	3.5
I-123 (13.27 h)	1.1	1.1	1.1	1.1	1.1	1.1
I-124 (4.176 d)	1.0	1.0	1.1	1.0	1.0	1.0
I-125 (59.4 d)	0.9	1.0	1.2	1.0	1.0	1.1
I-126 (12.93 d)	0.9	1.0	1.1	1.0	1.0	1.0
I-128 (24.99 m)	1.8	1.8	1.8	1.8	1.8	1.8
I-129 (1.57E7 y)	0.9	1.0	1.3	0.9	1.0	1.2
I-130 (12.36 h)	1.1	1.1	1.1	1.1	1.1	1.1
I-130m (8.84 m)	2.5	2.5	2.5	2.5	2.5	2.5
I-131 (8.0207 d)	1.0	1.0	1.1	1.0	1.0	1.0
I-132 (2.295 h)	1.2	1.2	1.2	1.2	1.2	1.2
I-132m (1.387 h)	1.3	1.3	1.3	1.3	1.3	1.3
I-133 (20.8 h)	1.0	1.1	1.1	1.1	1.1	1.1
I-134 (52.5 m)	1.5	1.5	1.5	1.5	1.5	1.5
I-134m (3.6 m)	3.6	3.6	3.6	3.6	3.6	3.6
I-135 (6.57 h)	1.1	1.1	1.1	1.1	1.1	1.1

Table 3 Comparison of Predicted Cumulative Activity in the Thyroid with a Blocked Thyroid, Based on the ICRP 56 Model

Age at injection	100 d	1 y	5 y	10 y	15 y	Adult
Thyroid						
This model (A)	1.4E+03	1.4E+03	1.4E+03	1.4E+03	1.4E+03	1.4E+03
Pub. 56 model (B)	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00	0.0E+00
Ratio A:B	infinite	infinite	infinite	infinite	infinite	infinite

The dosimetry system used in the ICRP's current dose coefficients for the public can be applied to assess the dosimetric implications of the proposed model for the thyroid. However, it is not fully compatible with the proposed model for non-thyroidal tissues due to it not addressing salivary glands as a source or target region. Table 4 compares dose coefficients for the normal thyroid following acute intake of selected iodine isotopes into the blood of an adult male, using the ICRP's current age-specific dosimetry system along with the proposed model and the ICRP Publication 56 model for systemic iodine. The ratios of dose coefficients for the thyroid from the two models align with the ratios of cumulative activity in the thyroid presented. This consistency arises because the thyroid dose from an iodine isotope is typically dominated by activity within the thyroid, with only a minor contribution from cross-irradiation by non-thyroidal tissues. The comparison of dose coefficients indicates that replacing the current model with the proposed one would have minimal impact on the age-related changes in dose coefficients for iodine isotopes. However, it does predict higher absolute dose coefficients for the thyroid, particularly for short-lived radioiodines like I-134. Table 5 show the dose coefficients for the acute intake of I-131 into the blood of an adult male were calculated using the updated dosimetry system, two scenarios were considered: a normal thyroid, where baseline transfer coefficients were applied for both biokinetic models, and a blocked thyroid. For the blocked thyroid, the ratio A:B of dose coefficients, based on the proposed and current models respectively, is notably large. These differences in the conversion of activity to dose primarily arise because, depending on the type of radiation emitted, there can be significant cross-irradiation of non-thyroidal tissues from a normal thyroid. In contrast, for a blocked thyroid, the dominant source of dose is self-dose to non-thyroidal tissues.

Table 4 Comparison of Age-Specific Dose Coefficients (Sv Bq^{-1}) for the Normal Thyroid Based on the ICRP 56 Model

Age at injection	100 d	1 y	5 y	10 y	15 y	Adult
I-131 (8.02 d)						
This model (A)	3.6E-06	3.6E-06	2.2E-06	1.1E-06	7.1E-07	4.5E-07
Pub. 56 model (B)	3.7E-06	3.6E-06	2.1E-06	1.1E-06	6.9E-07	4.4E-07
Ratio A:B	1.0	1.0	1.1	1.0	1.0	1.0

Table 5 Comparison of Dose Coefficients for I-131 of Iodine for Injection into Blood of an Adult Male Based on the ICRP 56 Model

Isotope and tissue	Applying baseline transfer coefficients of each model (Sv Bq^{-1})				Assuming no transfer to thyroid organic iodine pool (blocked thyroid) (Sv Bq^{-1})		
	(A) This model	(B) Pub. 56 model	Ratio A:B		(A) This model	(B) Pub. 56 model	Ratio A:B
I-131 (8.02 d)							
Thyroid	3.7E-07	3.6E-07	1.0		1.9E-09	4.9E-11	39
Stomach wall	3.5E-10	1.0E-10	3.5		4.3E-10	8.2E-11	5.2
Salivary glands	4.4E-10	2.7E-10	1.6		2.7E-10	1.3E-11	21
Red marrow	2.0E-10	2.4E-10	0.8		4.1E-11	9.0E-11	0.5
Liver	1.3E-10	1.1E-10	1.2		4.8E-11	8.7E-11	0.6
Kidneys	1.9E-10	8.9E-11	2.1		1.7E-10	8.7E-11	2.0

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