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Korean-specific biokinetic model for iodine in radiological protection

Tae-Eun Kwon[1,2], **Yoonsun Chung**[2] **and Young Woo Jin**[1]

[1] National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, 01812 Seoul, Republic of Korea
[2] Department of Nuclear Engineering, Hanyang University, 04763 Seoul, Republic of Korea

E-mail: ychung@hanyang.ac.kr

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Abstract

The International Commission on Radiological Protection (ICRP) recently adopted a detailed biokinetic model for systemic iodine with reference transfer coefficients based on typical worldwide dietary intakes of stable iodine. The regional data provided demonstrate that the ICRP reference thyroidal biokinetics may differ substantially across regions with atypically low or high dietary intakes of stable iodine. Importantly, the design of the ICRP model facilitates modifications of reference thyroidal kinetics based on regional dietary iodine intake. The present study extended the ICRP model to the South Korean population, whose dietary iodine intake is much higher than the global mean. The following three transfer coefficients were selected as targets for Korean-specific values: thyroidal uptake rate (λ_1), hormonal secretion rate (λ_4) and leakage rate of thyroidal organic iodine as inorganic iodide (λ_5). The Korean-specific values for λ_1, λ_4 and λ_5 were determined to be 4.48, 0.0086 and 0.0171 d^{-1}, respectively, to yield the measurements of thyroidal iodine and physiological status of Korean adults. The determined λ_1 and λ_5 values differed noticeably from the ICRP values, whereas the λ_4 value was comparable to that of the ICRP. Compared with the ICRP reference model, the Korean model, in which the Korean-specific transfer coefficients were adopted, predicted noticeably lower thyroidal uptake and faster decrease of thyroidal iodine. In addition, the predicted cumulative activities of radioiodine in the thyroid were substantially lower (40–80%) than those predicted by the ICRP model. The Korean model developed in this study demonstrates that the iodine biokinetics for Koreans

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(i.e. a population with a high iodine consumption) obviously differ from the prediction of the ICRP model. Hence, the Korean model may serve to improve the accuracy of thyroid dose estimation for Koreans and will lead to practical changes in matters concerned with radiological protection.

Keywords: Korean-specific, biokinetic model, iodine, dietary iodine, thyroid dose

(Some figures may appear in colour only in the online journal)

1. Introduction

Accurate prediction of the physiological behaviour of radioiodine in the body (i.e. the biokinetics of iodine) is a crucial challenge for the precise estimation of the internal dose that results from radioiodine intake. To improve the accuracy of predicted iodine biokinetics, the International Commission on Radiological Protection (ICRP) has developed and updated a biokinetic model for iodine. The simple model for iodine in ICRP 56 [1], composed of blood iodide, thyroid and the rest of the body, was used for decades, until a more advanced model was recently developed based on extensive data (figure 1) and adopted as a new reference biokinetic model in ICRP 137 [2].

However, despite the advances in the ICRP biokinetic model, applying the model to a particular population can result in considerable uncertainties due to inter-population variability. Specifically, the variation in iodine nutritional status caused by variations in dietary iodine can be attributed to significant discrepancies with regard to iodine biokinetics in the thyroid from that predicted using the ICRP model; for example, thyroidal uptake of iodide from the blood is adjusted by the level of iodine intake as a means of maintaining homeostasis of thyroid hormones [3] and thus can differ depending on dietary iodine levels. The model developer also pointed out the uncertainty of the biokinetic model arising from variations in dietary iodine [4] and provided various options for the calculation of case-specific biokinetic parameters considering dietary intake of stable iodine. Therefore, for populations in which dietary iodine is significantly different from the global mean, use of the ICRP reference model may cause significant uncertainty in the prediction of iodine biokinetics, thus resulting in critical misestimations of the actual thyroid dose.

South Koreans (referred to as Koreans hereafter) are known as a population with a high iodine consumption. Although the iodine status of Koreans has not been registered in the World Health Organization nutrition database [5], mean urinary iodine excretion for Koreans has been reported to range from 640 μg l^{-1} to 3800 μg l^{-1} [6], corresponding to a dietary iodine range of 1100 μg d^{-1} to 6600 μg d^{-1} based on an excreted fraction of ingested iodine of 0.92 [7] and a urinary excretion rate of 1.6 l d^{-1} [8]. Note that these values are much higher than the recommended nutrient intake of 150 μg d^{-1} [9]. Given that the reference dietary iodine intake used in the ICRP model is 160 μg d^{-1}, the high level of Korean dietary iodine will cause a significant discrepancy in iodine biokinetics from that predicted by the ICRP model.

Nevertheless, no studies on an iodine biokinetic model for the Korean population have been conducted. Although Kim *et al* [10] investigated the time-dependent behaviour of iodine, this study was based exclusively on observations without biokinetic interpretation. For practical applications in radiological protection, solid biokinetic parameters (i.e. transfer coefficients in the biokinetic model) representing Korean-specific iodine biokinetics must be developed. In addition, by utilising the advanced new biokinetic model in ICRP 137, the reliability for

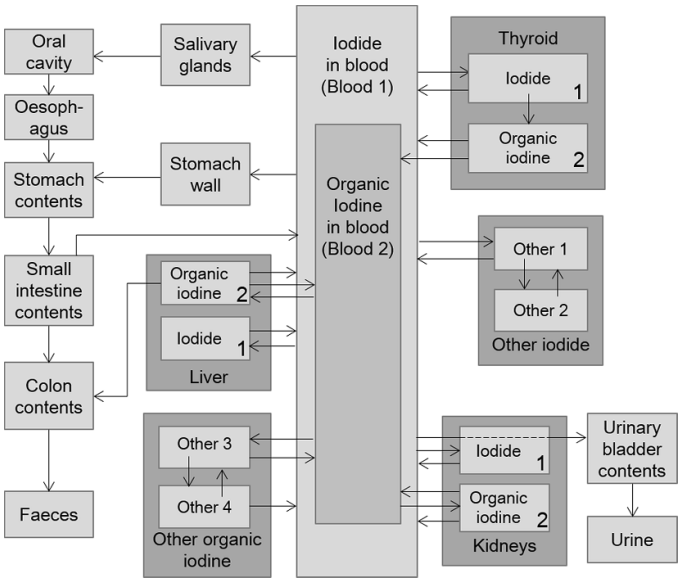

Figure 1. Structure of the ICRP reference biokinetic model for iodine in ICRP 137 [2].

prediction of iodine biokinetics can be improved and applications in radiological protection can be extended.

Therefore, the objective of this study was to extend the new ICRP reference model, which was developed based on worldwide data, to the Korean population, whose dietary iodine intake is noticeably high. This study summarises data on the biokinetics of iodine in Koreans based on a review of the ICRP model, and produces Korean-specific values for transfer coefficients that were expected to significantly differ from those in the ICRP model.

2. Materials and methods

2.1. Developmental review of the ICRP reference model

To identify transfer coefficients in the biokinetic model that should be, or can be, revised to Korean-specific values, the current ICRP reference model must be reviewed (figure 1). Although the model can be subdivided into three systems, namely thyroidal iodine, circulating inorganic iodide and extra-thyroidal organic iodine, in this study, when reviewing the model, we focused on the system of thyroidal iodine since the dose is delivered predominantly to the thyroid. The thyroidal iodine system comprises compartments of inorganic iodide and organic iodine in the thyroid or blood, which are linked by the transfer coefficients λ_1 to λ_5. As shown in figure 2, inorganic iodide in the blood (Blood 1) is trapped by the thyroid (Thyroid 1) at a rate λ_1. Trapped iodide returns to the blood at a rate λ_2 or is organically bound (Thyroid 2) at a rate λ_3. Organic iodine in the thyroid is immediately converted to thyroid hormones or secreted into the blood (Blood 2) at a rate λ_4. However, for high dietary iodine, organic iodine can be decomposed back into inorganic iodide within follicular cells and leak into the blood as inorganic iodide at a rate λ_5. The reference values for the transfer coefficients were obtained from collected experimental data or derived from the mass balance of iodine. The reference value for λ_1 (7.26) was derived from the assumption that uptake of iodide by the thyroid was

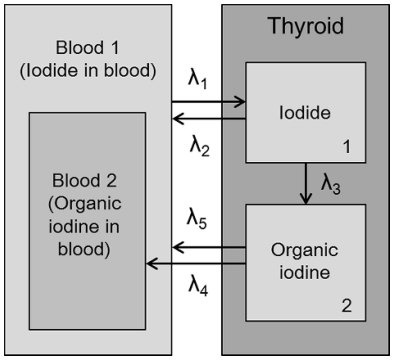

Figure 2. System of thyroidal iodine.

in mass balance with hormonal secretion of iodine. The reference value for λ_1 was calculated using nutritional data from the world population; λ_1 was suggested as a variable depending on the ratio of iodine dietary intake Y (μg d^{-1}) to thyroidal secretion of hormonal iodine S (μg d^{-1}); therefore, a λ_1 different from the reference value can be calculated when information on Y and S is available. The reference values for λ_2 and λ_3 were directly obtained from a human-based study [11] (95 and 36, respectively). The value of λ_4 (0.0077) was determined using the single-passage biological half-time in the thyroid (90 d), which was obtained from collected data; the corresponding apparent (externally measured) biological half-time was about 120 d. Note that single-passage biological half-time is different from the apparent biological half-time. Apparent half-time is longer than single-passage biological half-time due to the recycling of iodine back to the thyroid. The reference value for λ_4 is consistent with the ratio of the central estimate of daily hormonal iodine secretion (76 μg d^{-1}) to that of the mass of iodine in the thyroid (10 mg). Regarding λ_5, the ICRP model assumes that λ_5 is zero; in other words, it is assumed that all iodide decomposed from organic iodine is reused to produce thyroid hormones. It should be noted that a non-zero λ_5 is allowed only for high dietary intakes of stable iodine. If a non-zero value for λ_5 is used (i.e. in cases of high dietary iodine), λ_4 becomes S/C, where C (μg) is the mass of iodine in the thyroid, and λ_5 thus becomes the rest value (i.e. 0.0077 — S/C); however, this is based on the assumption that the single-passage biological half-time is 90 d.

2.2. Quantitative data on iodine for Koreans

2.2.1. Dietary intake of iodine. The latest nationwide epidemiological study on the iodine nutritional status of Koreans was conducted by Kim *et al* [12]. The daily iodine intake was evaluated based on urine iodine concentration (UIC) measurements from a large number of subjects ($n = 5908$). The extensive database established in the Korea National Health and Nutrition Examination Survey (KHNANES) 2013–2015 was used, and the accuracy of the correction of UIC to daily urine was improved by using individual-specific creatinine excretion rates, which were dependent on weight, age and sex. In this study, the mean daily iodine intake value estimated based on UIC measurements (780 μg d^{-1}) was adopted as the reference daily iodine intake of Koreans, which is approximately five times higher than the ICRP value (160 μg d^{-1}).

Table 1. Thyroidal uptake and apparent biological half-time in the thyroid of Koreans.

Variable		Observed values for Korean (mean ± SD)
Thyroidal uptake (% of ingested iodine)	2 h	6.88 ± 2.82
	4 h	10.44 ± 3.75
	6 h	13.31 ± 5.54
	24 h	19.70 ± 6.35
Apparent biological half-time (d)		37 ± 2.54

2.2.2. Thyroidal uptake and apparent biological half-time of iodine in the thyroid. For internal exposure to radioiodine, the thyroid dose is attributable predominantly to self-irradiation by beta-rays emitted from radioiodine in the thyroid itself. Thus, the most critical factors in thyroid dose estimation are the amount of iodine gathered in the thyroid and the time for which iodine remains in the thyroid. The sole study on thyroidal uptake and biological half-time of iodine in Koreans was conducted by Kim *et al* [10]. In his study, iodine-131 solution was orally administered to adult male Korean euthyroid subjects ($n = 28$) in their late 20s to early 30s and uptake of iodine by the thyroid was then measured using a NaI(Tl) detector. Measurement of urinary iodine was conducted for only the administered iodine-131 not stable iodine. Considering the large uncertainties associated with data obtained during the early phase [13], although thyroidal uptake values were reported at 2, 4, 6 and 24 h (table 1), only those for 24 h were used in the current study. The mean value of thyroidal uptake at 24 h was 19.7%, which is significantly lower than that predicted using the ICRP reference model (29%).

Ten volunteers from the subjects enrolled in the study performed by Kim *et al* [10] were followed for 60 d to evaluate the apparent biological half-time in the thyroid. The mean value of the apparent half-time in Koreans was 37 d, assuming no radioactive decay. Note that single-passage biological half-time may be shorter than 37 d. The observed apparent half-time in Koreans is similar to that in Japanese subjects (40 d) [14], but significantly lower than that predicted by the ICRP model (120 d) [2]. In this study, the 24 h thyroidal uptake value of 19.7% and the apparent half-time of 37 d were used as the reference Korean values.

To clearly evaluate the iodine biokinetics after reaching the circulatory system (e.g. inhalation or ingestion) regardless of the intake route, thyroid measurement data obtained from subjects who are intravenously administered with radioiodine are required. However, due to the absence of related data for Koreans, we used the data obtained from Korean subjects who were orally administered with a radioiodine solution, assuming that the initial absorption of ingested iodine into the blood was fast enough to ignore the difference in thyroidal uptake from that of injected iodine. This assumption is reasonable because ingested iodide is absorbed into the blood very quickly, at a rate of approximately 5% min^{-1} within 2 h [15]. In addition, the fact that the predicted amount of ingested iodine in the thyroid 24 h after intake corresponds to 29% of the injected iodine [4] also supports this assumption.

2.2.3. Concentration of hormonal iodine in blood plasma. The data on blood T_4 and T_3 concentrations need to consider the biokinetics of hormonal iodine. Generally, only free T_4 is measured for clinical purposes; however, some data on total T_4 and T_3 concentrations are available (table 2). Hormonal iodine concentrations were derived based on 65% and 59% weight per cent for T_4 and T_3, respectively. A total hormonal iodine concentration of 5.88 μg dl^{-1} was selected as the reference value for Koreans.

Table 2. Hormonal iodine concentration in the blood of Koreans.

Reference	N	Serum concentration (μg dl^{-1})		
		T_4	T_3	Hormonal iodine[a]
[16]	494 (282 male, 212 female)	8.90	0.13	5.86
[17]	199 (108 male, 91 female)	9.00	0.13	5.92
Total		8.93	0.13	5.88

[a] Calculated based on an iodine mass per cent values of 65% and 59% for T_4 and T_3, respectively

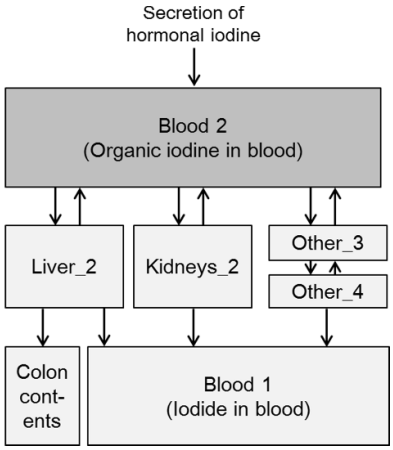

Figure 3. System of extra-thyroidal organic iodine.

2.2.4. Secretion rate of hormonal iodine. The secretion rate of hormonal iodine, S (μg dl^{-1}), which is expressed by the transfer from Thyroid 2 to the Blood 2 compartment, is directly related to the retention time of hormonal iodine in the thyroid. In this study, the rate of secretion of hormonal iodine in Koreans was inductively derived from an equilibrium calculation of extra-thyroidal organic iodine. Figure 3 shows the systemic model for extra-thyroidal organic iodine, extracted from the entire model for iodine. Using this model, the secretion of hormonal iodine can be simulated independently from the leakage of thyroidal iodine to the inorganic iodide pool. The secretion of hormonal iodine is represented as the entry to the blood plasma compartment, and the secretion rate in Koreans was determined as the value that yielded a hormonal iodine concentration at equilibrium with the Korean reference value, 5.88 μg dl^{-1}.

2.2.5. Inorganic iodide mass in the blood. The inorganic iodide mass in the blood, B_1 (μg), is another parameter required to predict the mass balance of iodine intake and excretion. B_1 can be calculated by the following mass balance equation, provided by Leggett [4]:

$$11.84B_1 = (Y - 0.02Y - 0.2S) \tag{1}$$

where 11.84 (d^{-1}) is the transfer coefficient of iodide from the blood to the urinary bladder and $0.02Y + 0.2S$ represents daily faecal excretion (i.e. 2% incomplete absorption from the alimentary tract of inorganic iodide plus 20% faecal excretion of hormonal iodine). In this study, the above equation was applied to Koreans based on the assumption that the renal clearance system of iodine for Koreans is similar to that described in the ICRP model.

Table 3. Target transfer coefficients for Korean-specific values.

From	To	Notation	Physiological mechanism	Decision criterion[a]
Blood	Thyroid_1	λ_1	Thyroidal uptake	① ② ③ ④
Thyroid_2	Blood_2	λ_4	Thyroidal hormone secretion	② ③ ④
Thyroid_2	Blood	λ_5[b]	Net result of transfer of organic iodine to inorganic iodide	① ② ③ ④

[a] Criterion: ① recommendation by the model developer, ② significance in dose estimation, ③ physiological validity, ④ compelling evidence (sufficient data).
[b] Non-zero only for high dietary iodine.

2.3. *Selection of transfer coefficients for Korean-specific values*

2.3.1. Decision criteria. It is neither possible nor reasonable to produce Korean-specific values for all the transfer coefficients in the biokinetic model. Producing Korean-specific values without validity and compelling evidence breaks the harmonisation of internal dosimetry and results in unnecessary uncertainty in the dose. Therefore, it is very important to reasonably select the target transfer coefficients for Korean-specific values based on scientific criteria. In this study, the following four criteria were established: (1) recommendations by the model developer; (2) significance in dose estimation; (3) physiological validity; (4) compelling evidence (sufficient data).

2.3.2. Target transfer coefficients. Based on these criteria, three transfer coefficients were selected as the target parameters for Korean-specific values (table 3).

As noted earlier, in the internal dosimetry of radioiodine the amount of iodine gathered in the thyroid and the retention time of iodine are most important. Thus, all selected transfer coefficients are involved in the system of thyroidal iodine (figure 2); this meets the second criterion. First, as noted in section 2.2, the transfer coefficient λ_1 has been suggested as a variable that could be calculated using the amount of dietary iodine and the secretion rate of hormonal iodine (criterion 1). The fact that λ_1 is dependent on the amount of dietary iodine supported the physiological validity of developing a Korean-specific value (criterion 3). Because λ_1 determines the amount of iodine gathered in the thyroid in the early phase after intake, thyroidal uptake measurements for Korean adults in the 2007 study of Kim *et al* [10] could be used to derive the Korean-specific value (criterion 4). The second selected parameter was the transfer coefficient λ_4, which is related to the biological half-time of iodine in the thyroid. Because the biological half-time in the thyroid is related to dietary intake and the size of thyroid stores of iodine [18], it is physiologically reasonable that the λ_4 value for Koreans may differ from the ICRP reference value (criterion 3). The apparent biological half-time for Koreans observed by Kim *et al* [10] provided compelling evidence for the need to derive a Korean-specific value (criterion 4). Lastly, according to the model developer, the transfer coefficient λ_5 can only have a non-zero value when there is a high intake of stable iodine (criterion 1). Leggett [4] addressed the non-zero λ_5 in terms of physiology (criterion 3); for example, leakage of the iodide released from monoiodotyrosine (MIT) and diiodotyrosine (DIT) may be large with a high dietary intake. Compelling evidence supporting a non-zero λ_5 for Koreans can be found not only in studies on the biological half-time for Koreans (see section 2.3.1) but also in the

data on the blood concentration of inorganic iodide in Japanese subjects, one of the populations with a significantly high iodine consumption (criterion 4). A non-zero λ_5 promotes the leakage of iodine from the thyroid, which consequently results in an increase in inorganic iodide in the blood. Mean values for inorganic iodide concentrations in sera from Japanese people were reported to be 3.8 μg dl^{-1} and 1.23 μg dl^{-1} [19, 20], which are much higher than the ICRP reference value of 0.27 μg dl^{-1}. There was no compelling evidence supporting changes in transfer coefficients other than the three explained above.

2.4. Determination of Korean-specific values

2.4.1. Blood-to-thyroid 1 rate (λ_1). The iodine that initially reaches the circulatory system is assigned to Blood 1 and then rapidly transfers to Thyroid 1 at a rate of λ_1. Because the amount of secreted iodine recycled back to the thyroid is trivial compared with the amount initially taken up, thyroidal uptake in the early phase after intake is mainly determined by λ_1. In this study, λ_1 was inductively derived from comparisons with the observed thyroidal uptake for Koreans. The Korean-specific value for λ_1 was determined to yield the reported thyroidal uptake of ingested iodine at 24 h (i.e. 19.7%). The biokinetic model was repeatedly implemented using increasing λ_1 values from 0 to 10 with 0.01 steps. For this, the human alimentary tract model and transfer coefficients for liquid type materials provided in the ICRP 100 [21] were used.

2.4.2. Thyroid 2-to-blood 2 rate (λ_4) and thyroid 2-to-blood 1 rate (λ_5). In the thyroidal iodine system, the leakage of iodine from the thyroid and the corresponding biological half-time in the thyroid are regulated by λ_2, λ_4 and λ_5. λ_2 is associated with prompt return to the blood without the binding process and, as noted earlier, is regarded not to be different between Koreans and the ICRP reference. Therefore, to simulate the Korean value of biological half-time in the thyroid (37 d), Korean-specific values should be assigned to λ_4 and λ_5. Thus, an appropriate value yielding the biological half-time of 37 d should be competitively apportioned to λ_4 and λ_5. Because the two values should be determined simultaneously, it is first necessary to find the relationship between λ_4 and λ_5. For this, the following mass balance equations in the thyroidal iodine system were established:

$$\lambda_3 T_1 = (\lambda_4 + \lambda_5)\, T_2 \tag{2}$$

$$\lambda_1 B_1 = (\lambda_2 + \lambda_3)\, T_1 \tag{3}$$

where T_1 and T_2 are the mass of inorganic iodide and organic iodine in the thyroid (μg), respectively, and B_1 is the mass of inorganic iodide in the blood (μg). The above equations were based on two assumptions: (1) thyroidal uptake of iodide is in mass balance with the sum of the prompt return to the blood of trapped iodide and the organic binding of iodide; (2) organic binding of iodide is in mass balance with the sum of the hormonal secretion of iodine and the leakage of organic iodine into the blood as inorganic iodide form. Equation 2 can be rearranged with the hormonal secretion of iodine S ($\lambda_4 T_2$) as follows:

$$\lambda_4 = \frac{S}{\lambda_3 T_1}\,(\lambda_4 + \lambda_5)\,. \tag{4}$$

Introducing T_1 from equation 3 into equation 4 yields the following equation:

$$\lambda_4 = \frac{S}{\lambda_3 \lambda_1 B_1}\,(\lambda_2 + \lambda_3)\,(\lambda_4 + \lambda_5)\,. \tag{5}$$

Because values other than λ_4 and λ_5 are already known, the constant K can be defined as

$$K = \frac{S}{\lambda_3 \lambda_1 B_1} (\lambda_2 + \lambda_3).$$

Then, the relation between λ_4 and λ_5 is finally written as

$$\lambda_5 = \frac{(1-K)}{K} \lambda_4. \tag{6}$$

Equation 6 shows that if the value of K is lower than 1, λ_4 and λ_5 are positively correlated, if not they are negatively correlated. Once the value of K is determined and the numerical relation between λ_4 and λ_5 is identified, Korean-specific values for λ_4 and λ_5 can be derived by repeatedly calculating the apparent biological half-time of iodine in the thyroid in a manner similar to that for λ_1. Time-dependent thyroidal iodine (i.e. the iodine content in Thyroid 1 and Thyroid 2) and the corresponding apparent half-time were repeatedly calculated with varying λ_4 and λ_5 values from 0 to 0.020 and from 0 to $0.020(1 - K)/K$, respectively. The values that yielded the apparent half-time for Koreans were determined as Korean-specific values for λ_4 and λ_5. Here, the apparent half-time was defined as the time required for thyroidal iodine to be reduced to half of that at 24 h; this is consistent with the study of Kim *et al* [10].

3. Results and discussion

3.1. Secretion rate of hormonal iodine and the inorganic iodide mass in the blood

To calculate the constant K, the daily secretion rate of hormonal iodine (S) and the mass of inorganic iodide in the blood (B_1) were first calculated. As a result of the equilibrium calculation of extra-thyroidal organic iodine, the unit secretion of hormonal iodine (i.e. entry into the blood of 1 μg d^{-1}) yielded an organic iodine concentration in blood plasma of 0.0858 μg dl^{-1}. Thus, the secretion rate, which yielded the Korean reference value of iodine concentration, was 68.5 μg d^{-1}. This value is not significantly different from the ICRP reference value of 64 μg d^{-1} [4]. This supports Leggett's findings that the mass of secreted hormonal iodine remains unchanged even at high levels of iodine intake [4]. Using the S and Y values for Koreans, the mass of inorganic iodide in the blood was found to be 63.06 μg based on equation 1.

3.2. Korean-specific transfer coefficients

Korean-specific transfer coefficients were determined based on data for Korean subjects. Thyroidal uptake of iodine 24 h after intake using increasing λ_1 values is shown in figure 4.

As λ_1 increases, the 24 h thyroidal uptake also gradually increases. From these results, the λ_1 value for Koreans corresponding to the observed value of 19.7% was determined to be 4.48 d^{-1}, which was less than two-thirds that of the ICRP reference value. To identify the relationship between λ_4 and λ_5, the constant K was calculated (0.335), indicating a positive relationship between λ_4 and λ_5. Consequently, increases in λ_4 from 0 to 0.02 corresponded to increases in λ_5 from 0 to 0.04. Calculated apparent half-times of iodine in the thyroid with increasing λ_4 and λ_5 are shown in figure 5. As λ_4 and λ_5 increased, the apparent half-time exponentially decreased from infinity to approximately 16 d. The Korean apparent half-time of 37 d was obtained when λ_4 and λ_5 were 0.0086 and 0.0171, respectively; therefore, these values were considered to be Korean-specific. The determined Korean-specific λ_4 value was

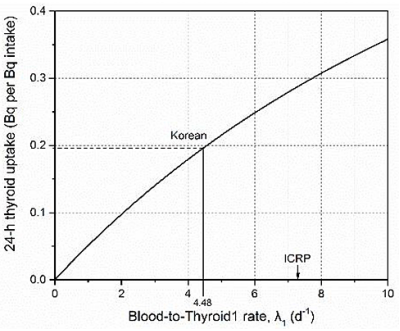

Figure 4. Calculated 24 h thyroidal uptake with increasing λ_1 value.

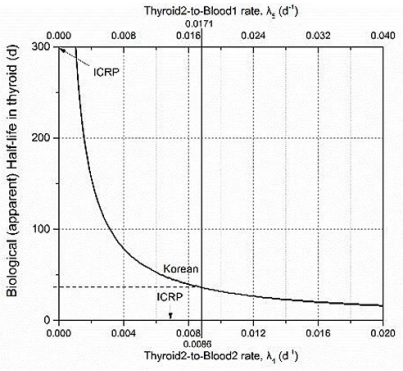

Figure 5. Calculated apparent biological half-time in the thyroid with increasing λ_4 and λ_5 values.

slightly higher than the ICRP reference value; however, the difference was not significant. Meanwhile, a noticeable difference was observed in our λ_5 value compared with the ICRP reference value. While λ_5 is set to zero in the ICRP model, the Korean-specific λ_5 has a value that is even higher than that of the Korean-specific λ_4 value.

The final Korean-specific transfer coefficients are listed in table 4.

The differences in our transfer coefficients directly result in considerable differences in the predicted iodine biokinetics in the body (see next section 3.3.). Among the Korean-specific transfer coefficients, the non-zero value of λ_5 was particularly important in the development of the Korean model. It is not practical to simulate the biological half-time in the thyroid for Koreans without adjusting the λ_5 value. When λ_4 is determined on the assumption that λ_5 is 0, the obtained value is 0.0245 d^{-1} (details not shown). In such a case, the iodine stores in the thyroid should be lower than 2800 μg to yield a secretion rate of hormonal iodine of 68.5 μg d^{-1} (i.e. iodine stores are 68.5 μg d^{-1}/0.0245 d^{-1}). Comparing the typical range of iodine content in the thyroid for the world's population (5–15 mg) [4] and that for Koreans (5.1–19.1 mg) [22], the calculated value for iodine stores is too low. Therefore, the non-zero λ_5 is an essential element for the realistic simulation of the iodine biokinetics for Koreans. Hereafter, the biokinetic model with Korean-specific transfer coefficients is regarded as the 'Korean model.'

Table 4. Korean-specific transfer coefficients.

From	To	Notation	Transfer coefficient (d^{-1})	
			Korean	ICRP
Blood	Thyroid_1	λ_1	4.48	7.26
Thyroid_2	Blood_2	λ_4	0.0086	0.0077
Thyroid_2	Blood	λ_5	0.0171	0

Table 5. Model prediction of mass and concentration of iodine at equilibrium.

Quantity	Predicted value (typical range or mean)	
	Korean	ICRP
Thyroidal iodine (μg)	8008 (4360–24 000)	8310 (5000–15 000)
Inorganic iodide in blood plasma ($\mu g\ dl^{-1}$)	1.46 (3.8 or 1.23)	0.27
Extra-thyroidal inorganic iodide (μg)	421	71
Organic iodine in blood plasma ($\mu g\ dl^{-1}$)	5.90 (5.88)	5.2 (3–8)
Extra-thyroidal organic iodine (μg)	689	640 (500–1000)

3.3. Model prediction

3.3.1. Mass or concentration of stable iodine at equilibrium. Model predictions of mass or concentration at equilibrium of thyroidal iodine, inorganic iodide and organic iodine in the blood, as well as inorganic iodide and organic iodine in extra-thyroidal pools, are listed in table 5 together with those from the ICRP model. When the typical mean value or the typical range were available they are shown together in parenthesis. No significant differences in the predicted values for thyroidal iodine were found, and the value for Koreans was within the typical range for Koreans [22]. However, the Korean model predicted an inorganic blood iodide concentration of 1.46 $\mu g\ dl^{-1}$, which is more than five times higher than that predicted by the ICRP model. Although direct validation with Korean data is not possible because there are no such data, the reported mean values of 3.8 $\mu g\ dl^{-1}$ and 1.23 $\mu g\ dl^{-1}$ for Japanese [19, 20] (shown earlier) support the validity of the noticeably high value predicted by the Korean model. The high blood iodide mass naturally led to a high mass of extra-thyroidal inorganic iodide. The mass of extra-thyroidal inorganic iodide was predicted to be approximately six times higher in the Korean model. Meanwhile, the organic iodine concentration in the blood and the mass of extra-thyroidal organic iodine predicted by the Korean model were not significantly different from those predicted by the ICRP model.

3.3.2. Time-dependent behaviour of iodine. The time-dependent levels of thyroidal iodine, the urinary excretion rate of iodine, extra-thyroidal organic iodine and inorganic iodide in the blood predicted by the Korean model are compared with those predicted by the ICRP model in figures 6–9. For comparison with the observed values, these predictions assumed no radioactive decay and oral ingestion of iodine solution. The observed values are shown too when available.

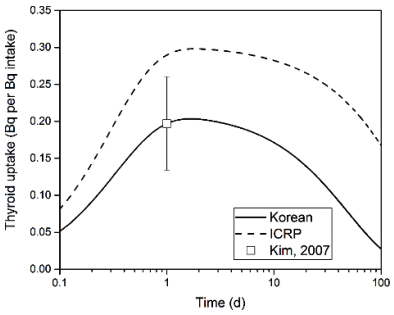

Figure 6. Model prediction of time-dependent thyroidal iodine level.

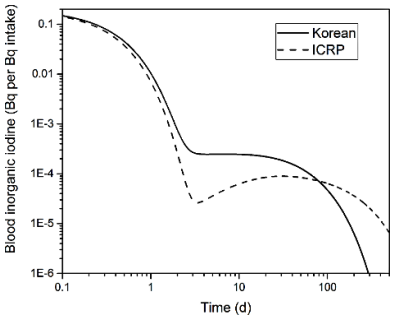

Figure 7. Model prediction of time-dependent inorganic iodide level in the blood.

As illustrated in figure 6, the Korean model predicted a time-dependent level of thyroidal iodine considerably lower than that predicted by the ICRP model. While the thyroidal iodine predicted by the Korean model (solid line) explains the value observed by Kim *et al* [10], the value predicted by the ICRP model (dashed line) is high enough to exceed the error bar of its standard deviation. The predicted thyroidal iodine peaks at 30% and 21% in the ICRP and Korean models, respectively, 24–30 h after intake. This difference is primarily due to differences in the λ_1 value. The lower λ_1 value in the Korean model leads to lower thyroidal uptake and greater transfer to organs or tissues other than the thyroid. In addition, the higher Korean-specific λ_4 and λ_5 values reduce thyroidal iodine much faster. Thus, while more than half of the maximum value of thyroidal iodine is expected to be present 100 d after intake in the ICRP model, only approximately one-tenth is expected to remain in the thyroid using the Korean model. These differences in the prediction of thyroid iodine directly influence the estimation of intake. The intake activity of radioiodine can be calculated by dividing the measured value of thyroidal iodine by the corresponding retention fraction in the thyroid (i.e. the amount retained in the thyroid after 1 Bq intake). Therefore, the lower time-dependent levels of thyroid iodine predicted by the Korean model may lead to higher intake estimations. In other words, even if an equal measured value is used, the intake activity of radioiodine will be higher when estimated with the Korean model. However, it should be noted that the final internal dose is calculated by multiplying the intake activity with internal dose coefficients. A lower level of thyroidal iodine in the Korean model may result in lower internal dose coefficients.

Inorganic iodide in the blood and extra-thyroidal organic iodine over time predicted by the Korean and ICRP models are shown in figures 7 and 8, respectively. As illustrated in figure 7, in the early phase after intake the inorganic blood iodide level predicted by the Korean model was

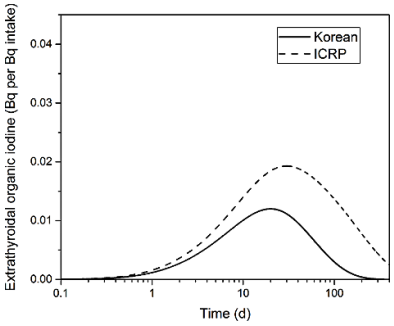

Figure 8. Model prediction of time-dependent extra-thyroidal organic iodine level.

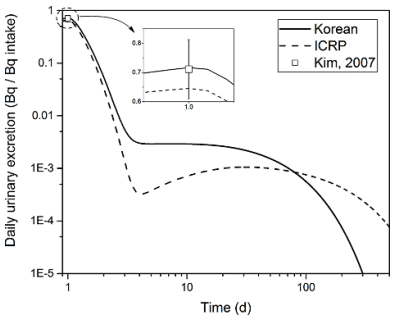

Figure 9. Model prediction of daily urinary excretion of iodine.

greater than that predicted by the ICRP model, and the difference was striking approximately 3 d after intake. The higher values in the Korean model during this period are probably due to the lower thyroidal uptake of iodine caused by the lower λ_1 and significant leakage as inorganic iodide from the thyroid caused by the non-zero λ_5. Moreover, considering that a smaller fraction of iodine is accumulated in the thyroid, a greater amount of inorganic iodide consequently enters the blood. However, after approximately 100 d, the two curves are observed to reverse. It is plausible that the higher λ_1 in the ICRP model results in longer retention of inorganic iodide in the blood through long-term recycling of blood iodide by the thyroid. Regarding the extra-thyroidal organic iodine, as shown in figure 8, the Korean model predicted considerably lower time-dependent levels compared with the ICRP model when the time exceeded a few days. Because of the non-zero λ_5, a considerable portion of thyroidal iodine leaks as inorganic iodide rather than organic iodine.

Figure 9 shows the daily urinary excretion rates of iodine. Since the sole supply to the urinary bladder is the inorganic iodide in the blood, the tendencies of the time-dependent levels of urinary excretions are similar to those of inorganic iodide in the blood shown above. As predicted for inorganic iodide in the blood, the Korean model predicted significantly faster daily urinary excretion until approximately 100 d after intake, after which the ICRP model predicted more excretion of iodine. The amount of iodine predicted by the Korean model to be excreted via urine during the first 24 h agrees with the observed value of 69%. Differences in prediction of the urinary excretion rate can be explained through differences in inorganic iodide in the blood.

Table 6. Comparison of predicted cumulative activity of radioiodine in the thyroid.

Isotope	Half-life	Korean model	ICRP model	Ratio
I-122	3.63 min	2.1E+00	3.3E+00	0.62
I-124	4.18 d	9.3E+04	1.5E+05	0.64
I-125	59.4 d	5.7E+05	1.5E+06	0.38
I-129	1.6E+07 years	9.0E+05	4.5E+06	0.20
I-131	8.02 d	1.7E+05	2.8E+05	0.60
I-132	2.3 h	9.9E−01	1.6E+00	0.62
I-134	52.5 min	1.6E+02	2.6E+02	0.63

Table 7. Comparison of predicted cumulative activity in non-thyroidal tissues (ratio of Korean value to ICRP value).

Isotope	Salivary glands	Stomach wall	Kidneys	Liver	Other[a]
I-122	1.00	1.00	1.00	1.00	1.00
I-124	1.14	1.14	1.09	0.88	1.09
I-125	1.19	1.19	0.60	0.45	0.60
I-129	1.07	1.07	0.31	0.23	0.30
I-131	1.16	1.16	1.02	0.77	1.02
I-132	1.00	1.00	1.00	1.00	1.00
I-134	1.02	1.02	1.02	1.02	1.02

[a] Blood plus soft tissues other than thyroid, salivary glands, stomach wall, kidneys and liver.

3.3.3. Cumulative activity of radioiodine. Relative comparison of the thyroid dose coefficients can be achieved by comparison of the cumulative activity of radioiodine in the thyroid. The cumulative activities (50 y integrated) of injected iodine in the thyroid calculated based on the Korean and ICRP models were compared for various radioisotopes and the results are shown in table 6.

For all radioisotopes, the cumulative activities in the thyroid calculated based on the Korean model were 40%–80% lower than those calculated based on the ICRP model. The difference was largest for I-129, which had the longest half-life.

The greater differences were shown for the longer-lived iodine, which is due to the greater impact induced by difference in the iodine biokinetics for longer-lived iodine isotopes. As for isotopes with a physical half-time much shorter than biological half-time, the observed decrease in the thyroid is caused primarily by radioactive decay rather than physiological clearance. These differences in cumulative thyroid activities indicate that even if an equal amount of radioiodine is inhaled or ingested, the thyroid exposure for Koreans may be significantly lower than that for the general global population.

Table 7 shows a comparison between the cumulative activities in non-thyroidal tissues calculated based on the Korean and the ICRP models in terms of their ratio.

For radioisotopes with short half-lives of up to a few days (i.e. I-122, I-124, I-131, I-132 and I-134), the Korean model predicted cumulative activities in all tissues similar to, or slightly higher than, the ICRP model. In contrast, for relatively longer-lived isotopes, the cumulative activities in the kidneys, liver and other tissues (blood plus soft tissues) were predicted to be significantly lower (up to by a factor of 0.29). These differences arise from the fact that short-lived isotopes exist in the blood primarily as inorganic iodide whereas longer-lived isotopes exist in the blood mainly as organic iodine [18]. In other words, the cumulative activities for short-lived iodine are attributable primarily to the decay of the inorganic iodide contained in

the organ or tissues whereas for longer-lived iodine they are mainly attributable to the decay of organic iodine. Therefore, considering that the Korean model predicted more inorganic iodide (shown earlier), the cumulative activities for short-lived iodine predicted by the Korean model were higher in all organs and tissues that involved inorganic iodide pools. In contrast, for relatively longer-lived iodine, since much less organic iodine was predicted in the Korean model, much less cumulative activity was predicted by the Korean model in organs that have a higher affinity for organic iodine, such as the kidneys and liver. The greater cumulative activities, predicted by the Korean model, in the salivary glands and stomach wall for longer-lived iodine (I-125, I-129) were caused by an absence of organic iodine pools in these organs.

3.3.4. Contribution and limitation of the Korean model. Differences between the Korean model and the ICRP model directly lead to differences in internal dosimetry of iodine and affect general matters concerning radiological protection. For instance, a difference in iodine internal dose can influence decision-making on the administration of thyroid blocking agents during a nuclear accident. The initiation of thyroid blocking is determined based on the predicted thyroid dose; for example, the US Food and Drug Administration [23] has recommended a predicted dose of 100 mGy as an intervention level for thyroid blocking. Since the Korean model predicts lower cumulative activities of radioiodine in the thyroid, it will derive higher intake activities corresponding to the intervention level. Therefore, the use of the Korean model allows for a margin regarding radioiodine intake to reach the standard for initiating iodine thyroid blocking measures. Regarding internal exposure monitoring for workers, the routine monitoring interval may need to be reselected due to the short biological half-time in the thyroid obtained in the Korean model. For example, the recommended monitoring interval for iodine-125 inhalation is generally 90 d; however, the use of the Korean model does not guarantee that the uncertainty introduced by the unknown intake time is no more than a factor of three for the monitoring interval. The proper monitoring interval, in which the assumption of intake at the mid-point time does not introduce an under- or over-estimation of more than a factor of three, is 60 d based on the Korean model (detailed calculation not shown). In addition, the use of the Korean model can instigate various changes in radiation safety regulation. The annual limit of intake (ALI) and derived air concentration (DAC) corresponding to dose limits must be recalculated, as differences in ALI and DAC are important for regulation of working areas, including the designation of controlled areas; meanwhile, application of the Korean model for regulatory purposes should guarantee conservative dose assessment and harmonisation of internal dosimetry. The Korean-specific dose estimation for radioiodine intake can provide a more reliable basis for epidemiological studies on thyroid cancer.

Nevertheless, the Korean model should be judiciously used. Specifically, the use of the value of thyroidal uptake and apparent biological half-time of iodine in the thyroid, reported by Kim *et al* (see section 2.2.2), as a reference for the entire Korean population needs further validation. The 24 h thyroidal uptake value reported by Kim *et al* (19.7%) shows a significant difference from the ICRP reference value (29%) but seems to be high compared with values presented in other studies involving subjects with a high dietary consumpton of iodine; for example, the mean value of 24 h thyroidal uptake in the studies of subjects with urinary iodine >300 μg d^{-1} was approximately 12% (see table 1 in [4]). Nevertheless, the value reported by Kim *et al* is considered representative of all Koreans, based on comparisons with studies involving Japanese subjects whose anatomical characteristics (e.g. thyroid volume), regional environment and dietary habits are similar to those of Koreans. In the Japanese, who consume a significantly high amount of dietary iodine (1000–3000 μg d^{-1}) [24], the reported thyroidal uptake values were 21% $\pm$ 8% between 1958 and 1967 [25] and 16.1% $\pm$ 5.4% in

the most recent (2020) study [26]; these values were comparable to those of the Korean population. Thus, considering these values in the Japanese population, it can be concluded that the thyroidal uptake value reported by Kim *et al* is within a predictable range for all Koreans as well. In addition, although 19.7% appears high, using this value for radiological protection can be considered the best option, as a higher thyroidal uptake may lead to conservative dose estimation.

Therefore, the reference values for the thyroidal uptake and biological half-time in Koreans should be consistently updated with extensive measurements in the future to improve the accuracy of prediction of Korean-specific thyroid biokinetics.

4. Conclusions

This study attempted to develop a Korean-specific biokinetic model for iodine to reduce the uncertainty introduced by inter-population variability arising when the ICRP reference model is applied to a particular population. The three transfer coefficients (i.e. the transfer coefficients for thyroidal uptake and clearance) determined based on Korean data were significantly different from the ICRP reference values, and the time-dependent iodine level and cumulative activities in the body predicted by the Korean model also showed substantial differences from those predicted by the ICRP model, implying that the actual thyroid dose for Koreans may be mis-estimated when using the ICRP model.

Based on the results of the current study, subsequent studies are being designed to calculate dosimetric data (i.e. bioassay functions and dose coefficients) for internal dosimetry of iodine in Koreans. Moreover, to improve the practical applications for radiological safety, guidance with respect to radioiodine intake and the resultant dose for Koreans will be provided in tabular or graphic form. In addition, the protective effect of thyroid blocking agents should be re-evaluated based on the Korean model, as differences in the thyroidal uptake rate can result in differences in efficacy and duration of thyroid blocking agent treatment. Lastly, the Korean model should be extended to other age groups based on iodine biokinetic data in the immature Korean body, and subsequent age-specific dosimetric data must be calculated.

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Conficts of interest

The authors have no conflicts of interest to declare.

ORCID iD

Tae-Eun Kwon https://orcid.org/0000-0002-7252-4634

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