



## Original Article

## Application of the new ICRP iodine biokinetic model for internal dosimetry in case of thyroid blocking

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## ABSTRACT

Administration of stable iodine has been considered a best measure to protect the thyroid from internal irradiation by radioiodine intake, and its efficacy on thyroid protection has been quantitatively evaluated in several simulation studies on the basis of simple iodine biokinetic models (i.e., three-compartment model). However, the new iodine biokinetic model adopted by the International Commission on Radiological Protection interprets and expresses the thyroid blocking phenomenon differently. Therefore, in this study, the new model was analyzed in terms of thyroid blocking and implemented to reassess the protective effects and to produce dosimetric data. The biokinetic model calculation was performed using computation modules developed by authors, and the results were compared with those of experimental data and prior simulation studies. The new model predicted protective effects that were generally consistent with those of experimental data, except for those in the range of stable iodine administration –72 h before radioiodine exposure. Additionally, the dosimetric data calculated in this study demonstrates a critical limitation of the three-compartment model in predicting bioassay functions, and indicated that dose assessment 1 d after exposure would result in a similar dose estimate irrespective of the administration time of stable iodine.

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## 1. Introduction

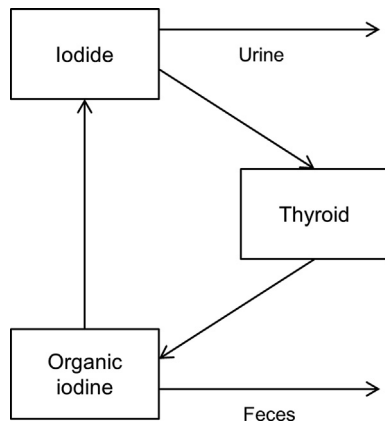
Reduction of thyroid irradiation from radioiodine intake is one of the main concerns regarding radiation protection in the event of nuclear accidents. This can be achieved with stable iodine (e.g., potassium iodide, KI) administration, which has been recommended as the best measure for thyroid blocking of iodine by the World Health Organization (WHO) [1]. The protective effect (e.g. averted dose) of KI administration has been demonstrated in extensive human-based experiments, and it is generally known that timely administration of KI in appropriate amounts (50–100 mg in adults) almost completely blocks thyroid uptake of radioiodine [2]. In practical situations, however, timely administration of KI, coinciding with radioiodine intake, is rarely possible because of the vagaries in radioiodine release and dispersion. Thus, complete blocking is not practical. Furthermore, although thyroid dose estimation should be carried out appropriately, it is also

difficult because the physiological behavior of incorporated radioiodine is no longer normal after the KI administration.

Until now, several simulation studies on the basis of biokinetic model calculation have been conducted to prospectively estimate protective effects [3–6] according to KI administration time relative to radioiodine exposure. More recently, the thyroid dosimetry data that can be used for thyroid blocking was also calculated and provided as a correction factor [7]. However, because the biokinetic models that were used in prior studies (Fig. 1) included only three (or four) compartments (referred to as a three-compartment model in this paper), they had limitations in specifying the complicated iodine biokinetics. For instance, the iodine concentrations in the blood and in other alimentary tract secretions could not be distinguished in the three-compartment model, despite actual differences of 20–40-fold [8]. Moreover, because the thyroidal iodine was represented as only a single compartment, the detailed intrathyroidal biokinetics could not be expressed, and the thyroid blocking mechanism was thus postulated as directly prohibiting thyroidal uptake of iodine. The issues that arise from oversimplified compartments can be resolved by extending and segmenting the compartments and thus adopting the new International

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**Fig. 1.** Three-compartment biokinetic model for iodine used in previous simulation studies.

Commission on Radiological Protection (ICRP) biokinetic model.

Recently, a more elaborate model was developed by Leggett [8] and adopted as a new ICRP reference biokinetic model [9]. The new model facilitated a more sophisticated and practical description of iodine biokinetics by remarkably extending the number of compartments, and especially resulted in an important difference in the interpretation of the thyroid blocking mechanism (explained later in detail). Therefore, the new model can simulate the thyroid blocking phenomenon in a different manner and might provide different assessments of the effect of KI administration on thyroid blocking. This new biokinetic model and the significant change in thyroid blocking interpretation have already been applied to reference dose coefficient calculations [10] and for individual dose assessment in a patient whose thyroid was incompletely blocked [11]. In particular, the application of the new model for developing a practical dose assessment method allowed retrospective estimation of the individual thyroid blocking level [12].

However, the previous work of the author assumed a constant intra-thyroidal organification rate (described later) and focused on the introduction of the new dosimetry method rather than assessing the feasibility of the new model for thyroid blocking. Thus, it is still necessary to apply the new model in a more general approach, such as the protective effect calculation considering KI administration time, by means of time-dependent organification rate to investigate the effect of the model change on understanding the iodine prophylaxis.

Hence, the first purpose of this study was re-evaluating the thyroid protective effect of KI administration using the new iodine biokinetic model. Protective effects, according to administration mass and time, were calculated and compared with those in the aforementioned experiments and simulation studies. Furthermore, dosimetric data (e.g., thyroid retention functions, dose coefficients, and dose per content functions) according to the KI administration time were also calculated and compared with those of the recent simulation study that used the three-compartment model.

## 2. Materials and methods

### 2.1. Brief description of thyroid blocking mechanism

Reduction of thyroid irradiation by stable iodine administration is essentially achieved by reducing the amount of accumulated radioiodine in the thyroid. The sufficient amount of stable iodine saturates the iodide transport mechanism of the thyroid and competes with radioiodine for transport via the sodium iodide

symporter. In addition, acute administration of a large mass of stable iodine may lead to almost complete inhibition of the intra-thyroidal organification of iodide (acute Wolff-Chaikoff effect) [13] and thus may promote excretion. The thyroid generally recovers from the Wolff-Chaikoff effect within a few days, and intrathyroidal iodide organification resumes.

### 2.2. New ICRP reference model for iodine

The most important feature of the new ICRP model (Fig. 2), compared with the previous three-compartment model (Fig. 1), is the number of compartments, which has remarkably increased by specifying and subdividing the iodine compartments. Extra-thyroidal 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. In particular, separation of the blood compartment from those for other secretions allows the blood iodide content to be calculated directly and more accurately. Because the extent of uptake blockade may be strongly related to serum inorganic iodide [14], accurate calculation of blood content can improve the reliability of the thyroid blocking simulation. In addition, inorganic iodide and organic iodine compartments were chemically separated and thus single organs were physically subdivided again into inorganic and organic compartments. This chemical state specification facilitated a more detailed description of iodine behavior and iodine biokinetics within the thyroid (expressed only by absorption to the thyroid and secretion as organic iodine in the three-compartment model). In the new model, trapping (the uptake into the thyroid) and binding (organification in the thyroid) could be mathematically distinguished; therefore, unbound inorganic iodide could return to the blood without long retention, and organically bound iodine is also allowed to leak into the inorganic blood compartment in case of high dietary levels.

### 2.3. Implementation of thyroid blocking in the new model

The detailed description of the thyroid biokinetics makes a very significant difference in the implementation of thyroid blocking. While the thyroid blocking mechanism was postulated to directly reduce the uptake of iodine into the thyroid in previous simulation studies (as noted in the previous section), it is now represented by inhibiting the intrathyroidal organification of iodide; this was clearly noted in the model developer paper [8]. This is on the basis of the assumption that acute intake of a sufficient amount of stable iodine leads to near complete inhibition of hydrogen peroxide ( $H_2O_2$ ) generation, which is required for thyroid hormone synthesis. In the current study, the thyroid blocking phenomenon was therefore implemented by reducing the Thyroid 1-to-Thyroid 2 rate rather than the Blood-to-Thyroid rate. In accordance with this interpretation, ICRP also set the Thyroid 1-to-Thyroid 2 rate to zero to simulate complete thyroid blocking, although complete blocking cannot be practically attained. However, because the thyroid blocking phenomenon recovers on the basis of continuous thyroid autoregulation, the Thyroid 1-to-Thyroid 2 rate is not considered a constant value but a variable that recovers gradually to a normal value ( $95\text{ d}^{-1}$ ). Whereas continuous recovery was expressed in terms of thyroidal iodine content in the early studies [3,4], it was considered a function of serum iodide concentration in more recent studies [5,6], on the basis of the human data from the study by Blum and Eisenbud (1967) [14]. Blum and Eisenbud derived an empirical equation of 24-h thyroid uptake relative to the iodide serum concentration, as demonstrated in eq. (1).

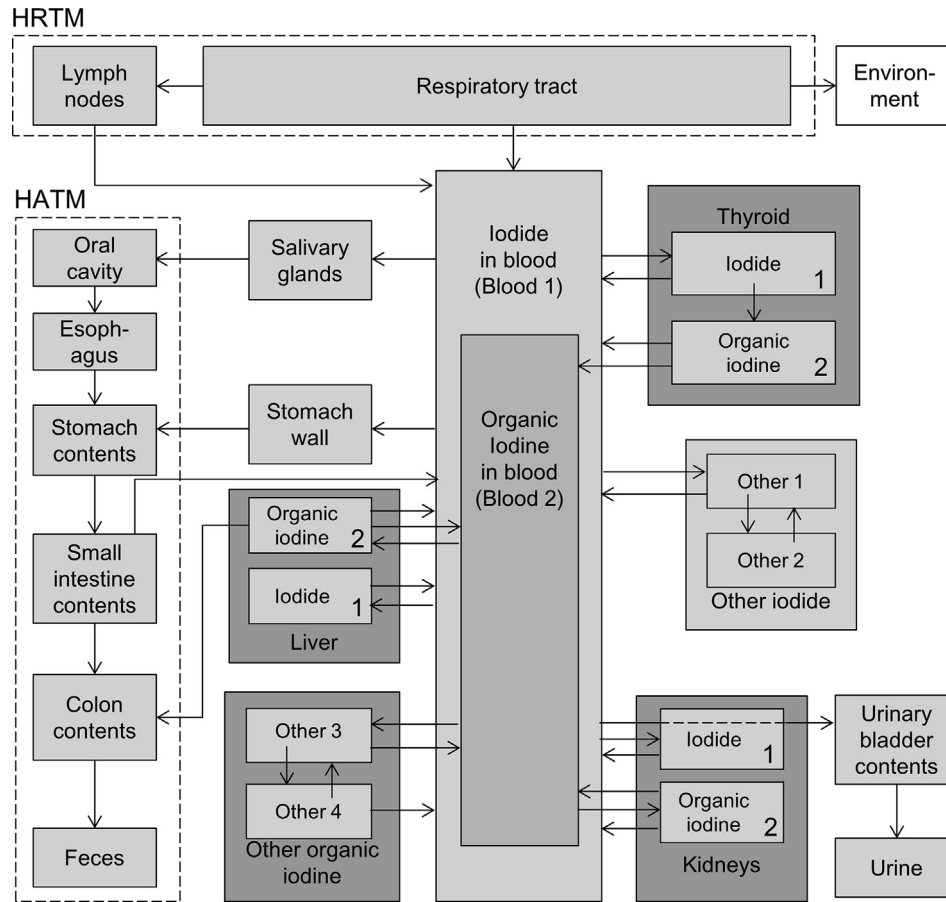


Fig. 2. New biokinetic model for iodine (Leggett 2010, ICRP 2017) with the human alimentary tract model (ICRP 2006) and the human respiratory tract model (ICRP 2015). ICRP, International Commission on Radiological Protection.

$$\text{Thyroid uptake suppression} = 0.377 I_{\text{serum}}^{-0.9} \quad (1)$$

Thyroid uptake suppression = 24-h thyroid uptake/maximum of 24-h thyroid uptake.

$I_{\text{serum}}$  = inorganic iodide concentration in serum ( $\mu\text{g/dL}$ ).

To link the transfer rate of Thyroid 1-to-Thyroid 2,  $r_{Th}$ , to the serum inorganic iodide concentration, the correlation between 24-h thyroid uptake and  $r_{Th}$  was deduced using the biokinetic model calculation, which has been explained subsequently; linearity was also confirmed (details not shown here). On the basis of the linearity and eq. (1), we have established the following equation that relates the  $r_{Th}$  to the serum inorganic iodide concentration:

$$r_{Th} = r_{Th-max} 0.377 I_{\text{serum}}^{-0.9} \quad (2)$$

where,  $r_{Th-max}$  (77.52) is the nominal value of maximum Thyroid 1-to-Thyroid 2 transfer rate at a serum iodide concentration of zero. The  $r_{Th-max}$  value can be derived using the corresponding  $r_{Th}$  and  $I_{\text{serum}}$  of the normal state (i.e.,  $r_{Th}$  of  $95 \text{ d}^{-1}$  and  $I_{\text{serum}}$  of  $0.27 \mu\text{g dL}^{-1}$ ) [8].

#### 2.4. Alimentary and respiratory tract model

The ICRP human alimentary tract model [15] and human respiratory tract model [16] (Fig. 2) were used to calculate the blood uptake fraction over time of orally ingested stable iodine and inhaled radioactive iodine, respectively. In the case of iodine exposure via inhalation, the particle size was assumed to be  $1 \mu\text{m}$

for the public. In this study, environmental exposure (indoor at home) was assumed, and corresponding deposition fractions were used in the respiratory tract model.

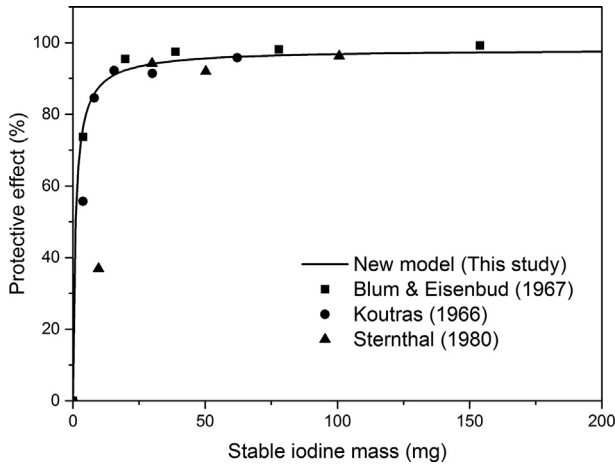
#### 2.5. Calculation of protective effect

Thyroid blockade effectiveness is generally assessed through the protective effect, which is defined as an averted dose. The protective effect can be calculated using the following equation.

$$\text{Protective effect} = \frac{D_0 - D_{adm}}{D_0} \quad (3)$$

where  $D_0$  and  $D_{adm}$  are the thyroid doses with and without blocking, respectively. In previous simulation studies, the protective effects were calculated as reduction ratios of 24-h thyroid uptake and the number of iodine disintegration in the thyroid, with the assumption that an effect of extrathyroidal iodine on thyroid dose is negligible; however, in the current study, protective effects were calculated directly by the reduction of thyroid dose (i.e., reduction of dose coefficients with and without thyroid blocking).

In this study, protective effects were calculated as a function of stable iodine amount with up to 200 mg of stable iodine (260 mg of KI) or as a function of administration time from 96 h before and up to 24 h after expected onset of radioiodine exposure for 100 mg of stable iodine (i.e., 130 mg of KI), which is recommended as single dosage for adults and adolescents [1]. By default, the protective effect was calculated for I-131 (half-life of 8.02 h).



**Fig. 3.** Protective effects for I-131 intake as a function of stable iodine amount. The original experimental data were reported as 24-h thyroid uptake but converted to protective effect value in this study.

2.6. Calculation of dosimetric data

To calculate the dosimetric data (e.g., thyroid retention functions and dose coefficients), it is first necessary to mathematically express the biokinetic model. The aforementioned biokinetic models were written as a set of first-order differential equations, such as eq. (4), where  $q_i$  is the activity of iodine in the  $i$ -th compartment, and  $r_{ij}$  is the transfer rate from  $j$ -to  $i$ -th compartment.

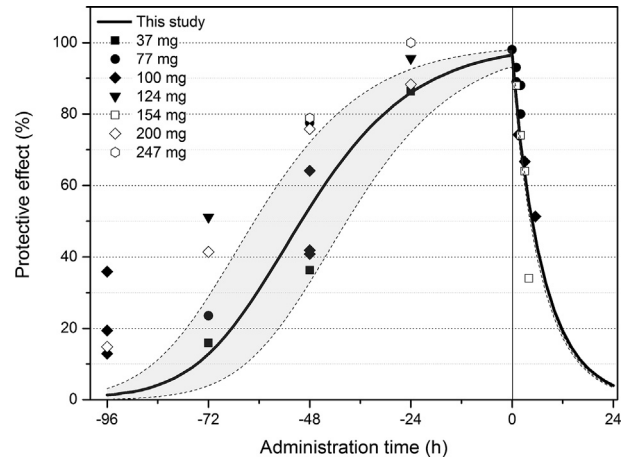
$$\frac{dq_i}{dt} = \sum_{j=1, j \neq i}^N r_{ij}q_j - q_i \sum_{j=1, j \neq i}^N r_{ji} \quad (4)$$

The equations were solved by matrix algebra, and calculated sequentially with a constant time step. The calculation time step was adjusted as 1 h (0.04 d) to secure continuity of the physiological behavior of iodine, and the Thyroid 1-to-Thyroid 2 rate was repeatedly derived by eq. (2) and substituted in each calculation step. The steady-state amounts of iodine were set at a normal dietary intake of  $160 \mu\text{g d}^{-1}$  [8]. Thyroid equivalent dose coefficients,  $h_{\text{Thyroid}}(50)$  (Sv/Bq), may be calculated by the following equation:

$$h_{\text{Thyroid}}(50) = \sum_S U_S(50) \text{SEE}(\text{Thyroid} \leftarrow S) \quad (5)$$

where  $U_S(50)$  is integrated number of radioiodine transformation per unit activity intake in source organ  $S$  for 50 years, and  $\text{SEE}(\text{Thyroid} \leftarrow S)$ , specific effective energy (Sv (Bq s) $^{-1}$ ), is equivalent dose in thyroid per transformation in source organ  $S$ . SEE can be calculated by combining the SAF (specific absorbed fraction) with other fundamental data. In this study, SAF values provided in ICRP publication 133 [17] were used to employ the ICRP reference voxel phantom [18]. Other detailed information was employed in accordance with ICRP publication 103 [19]. To calculate thyroid retention functions and dose coefficients, we developed computation modules; these have already been verified by comparison with ICRP reference bioassay functions and dose coefficients without stable iodine administration, in a previous study [12].

The thyroid retention functions and equivalent dose coefficients were calculated according to the KI administration time and compared with those of Broggio et al. as a representative of studies that used the three-compartment model because the work of Broggio et al. provided sufficient data for the comparison. However,



**Fig. 4.** Protective effects for I-131 intake as a function of administration time (compared with experimental data). The 0 h time refers to the exact coincidence of administration with exposure. The range of calculated protective effects from 37 mg to 247 mg was expressed by the shadow area between dash lines. When numerical data were not available, the data were graphically extracted.

more intuitive interpretation with respect to dose assessment can be obtained from the dose per content functions (DPCFs), which are derived by dividing the dose coefficients by the thyroid retention functions. The thyroid dose can be then calculated directly by multiplying the DPCF with the thyroid measurement value; this implies that when measurement results are equal, the same DPCF values lead to same thyroid dose estimates. In this study, DPCFs also were calculated and compared. By default, the dosimetric data were calculated for I-131 inhalation with F-type for absorption to blood.

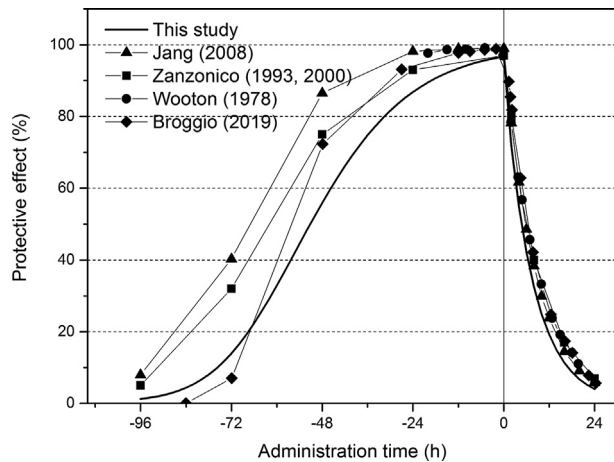
3. Results

3.1. Protective effects

Protective effect as a function of KI amount was calculated and compared with experimental data [14,20,21] in which various KI amounts were administered simultaneously with the radioiodine intake (Fig. 3). The protective effects dramatically increased as the amount of stable iodine approached 30 mg, which was sufficient to block thyroid uptake almost completely (90%). Above 50 mg of stable iodine, there was not much additional effectiveness. The calculated protective effect (solid line) matched well with human-based experiments.

Fig. 4 shows the calculated protective effect curve as a function of administration time relative to radioiodine exposure, which was overlaid with a variety of experimental results [3,14,22]. Owing to the limited number of experiments, the expansive experimental data for which at least 37 mg of stable iodine was administered, were cited (in consideration of similar protective effect in the dosage above 30 mg, as previously noted). Although statistical analysis was not performed, it can be confirmed that the correlation between protective effect and administration time as generally known was well illustrated by the calculated protective effect curve. While stable iodine administration before exposure ( $t < 0$  h) showed prolonged efficacy, administration after exposure ( $t > 0$  h) dramatically reduced the protective effects as KI administration was delayed. Considering the large uncertainty of experimental data, the protective effects that were calculated in the current study seem to agree well with those reported in experimental studies, except for the KI administration at times greater than 72 h before





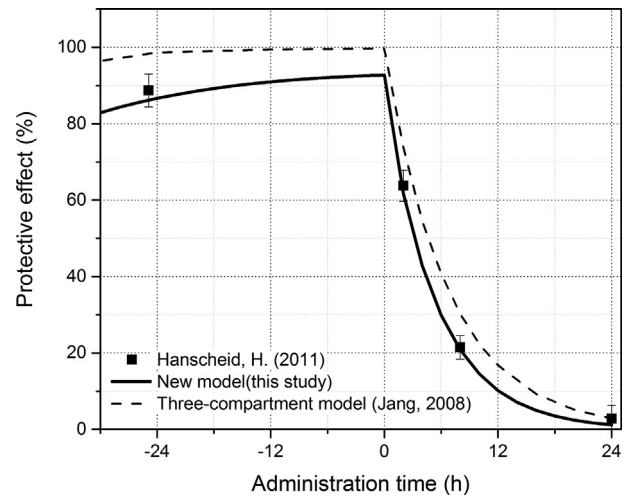
**Fig. 5.** Protective effects for I-131 intake as a function of administration time (compared with other simulation studies that used the three-compartment biokinetic model). The 0 h time refers to the exact coincidence of administration with exposure.

exposure. The protective effects in the left side of  $-72$  h showed significant discrepancies with experimental data in protective effect. Although the calculated protective effect at  $-96$  h was almost zero (1.2%), the experimental results were still higher than 10%. Similar issues were also seen in the comparison with other simulation studies that used the three-compartment biokinetic models (Fig. 5). Although calculated protective effect curves have similar tendencies, the protective effect curve of this study (bold line) was significantly lower than those of other simulation studies. In particular, the differences in the range of administration prior to exposure were striking; for example, there was a 30–40% difference at  $-48$  h. As an exception, the protective effects that Broggio et al. calculated dropped dramatically when the administration time was  $-70$  h or earlier, but the exact cause of this was not fully explained in their paper.

A more precise comparison could be implemented with the most recent human-based experiment, in which KI of 100 mg was administered 24.9 h before or 2, 8, and 24 h after I-123 (half-life of 13.27 h) injection [23]. In the investigation, data of thyroid dose reduction was collected for seven subjects in each point, and thyroid uptake measurement was conducted very precisely while considering individual-specific thyroid depth. As shown in Fig. 6, high consistency of the protective effects observed in this study was conformed. The protective effect curve in this study almost exactly corresponds to the experimental results within a standard deviation. The dash line in Fig. 6 represents the protective effect curve for I-133 (half-life of 20.8 h) that Jang et al. calculated using the three-compartment model. Although the protective effects of I-123 and I-133 were predicted to be similar because of the similar half-life, the protective effects observed in the study by Jang et al. were remarkably higher; therefore, the results derived from the three-compartment model were inconsistent with experimental data.

### 3.2. Dosimetric data

In Fig. 7, the thyroid retention functions according to administration time calculated using the new model in this study were compared with those that calculated using the three-compartment model. For KI administration prior to radioiodine exposure (Fig. 7(a)), the thyroid retention functions show significantly different values and tendencies depending on the used biokinetic model. The thyroid retention functions of the three-compartment model (dash lines) start at vastly different points according to the



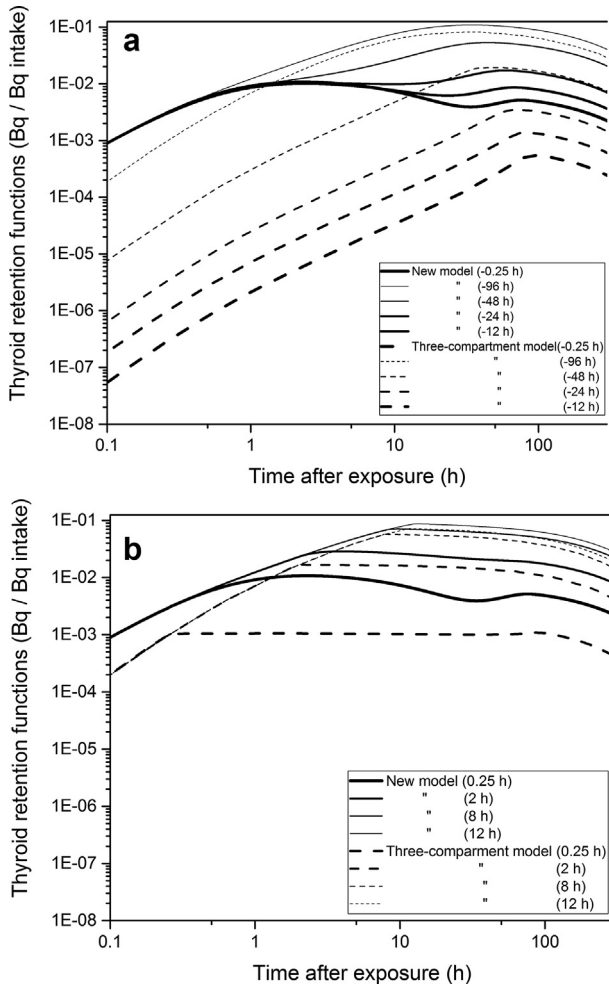
**Fig. 6.** Precise comparison of the calculated protective effects with the experiment in which I-123 (half-life: 13.27 h) was administered. The solid line (this study) and the dash line (Jang et al. [5]) were calculated for I-123 and I-133 (half-life: 20.8 h), respectively. The nuclides with similar half-life were expected to produce similar results.

administration time, but the shapes of all curves are similar. On the contrary, the thyroid retention functions of the new model (solid lines) start at a single point regardless of the administration time and begin to vary after 0.5 h in different shapes. It is also apparent that the absolute differences in thyroid retention functions of the two models are largest within 1 h after exposure. On the other hand, when KI was administered after exposure (Fig. 7(b)), the maximum differences in thyroid retention functions were within 40% and the decrease tendencies after KI administration are similar.

Thyroid equivalent dose coefficients calculated using both biokinetic models were also shown in Fig. 8. In this study, the dose coefficients were calculated for adult males and adult females separately using gender-specific voxel phantoms, and the dose coefficients of females were slightly higher than those of males because of the lower thyroid mass of females. Comparing the dose coefficients for male, the both biokinetic models produced very similar dose coefficients when KI was administered after exposure (difference within 10%), whereas when KI was administered before exposure the dose coefficients differed more than a factor of two; the pattern of the difference was the opposite of the result of the protective effect comparison.

Fig. 9 shows the DPCFs according to the administration time. As with the comparison of thyroid retention functions, the difference depending on the biokinetic model in DPCFs (i.e., between solid lines and dot lines) was noticeable for KI administration prior to exposure (Fig. 9(a)). In particular, as the KI administration time and dose assessment times are nearer to exposure, the difference becomes more striking. For instance, when KI is administered 12 h prior to the exposure, DPCF at 10 h after exposure of the three-compartment model (thinnest dash line) was more than 100 times higher than that of the new model (thinnest solid line); this means that the equal measurement can address 100 times different dose estimate. Conversely, for KI administration after exposure (Fig. 9(b)), the difference was not significant, depending on the biokinetic model. The DPCF without stable iodine administration, calculated using the new model, was drawn together for comparison; as shown in Fig. 9(a), it overlapped with that of  $-96$  h.

The full data of thyroid retention functions, dose coefficients and DPCFs for other isotopes and chemical forms are available, upon request, from the author, T.-E. Kwon (ktgrace@kirams.re.kr).

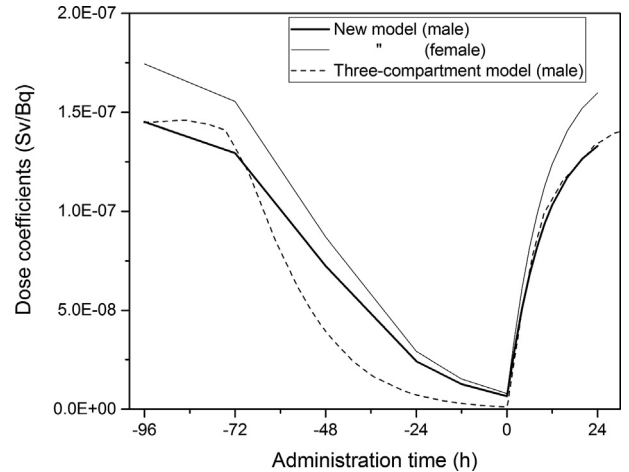


**Fig. 7.** Thyroid retention functions for I-131 according to stable iodine administration time for inhalation of I-131 particulates with absorption type F (for administration prior to (a), or after (b) radioiodine exposure).

**4. Discussions**

The new ICRP biokinetic model derived the protective effects that generally correspond to the experimental data, except for the case when KI was administered too early. The discrepancies in the range of administration at times greater than 72 h before radioiodine intake indicate that the prolonged efficacy of thyroid blockade cannot be fully explained by inhibiting thyroidal organification alone. Because thyroid iodine organification resumes within two or three days (escape from Wolff-Chaikoff effect), additional adjustments in biokinetic model calculation beyond reducing the Thyroid 1-to-Thyroid 2 rate are necessary to simulate the prolonged efficacy more practically. Representation of the thyroid blocking phenomenon by both, Blood-to-Thyroid 1 and Thyroid 1-to-Thyroid 2 transfer rates, and adjusting the relation between thyroid uptake and serum iodide concentrations (i.e., eq. (1)) based on further research, may improve prolonged efficacy simulation.

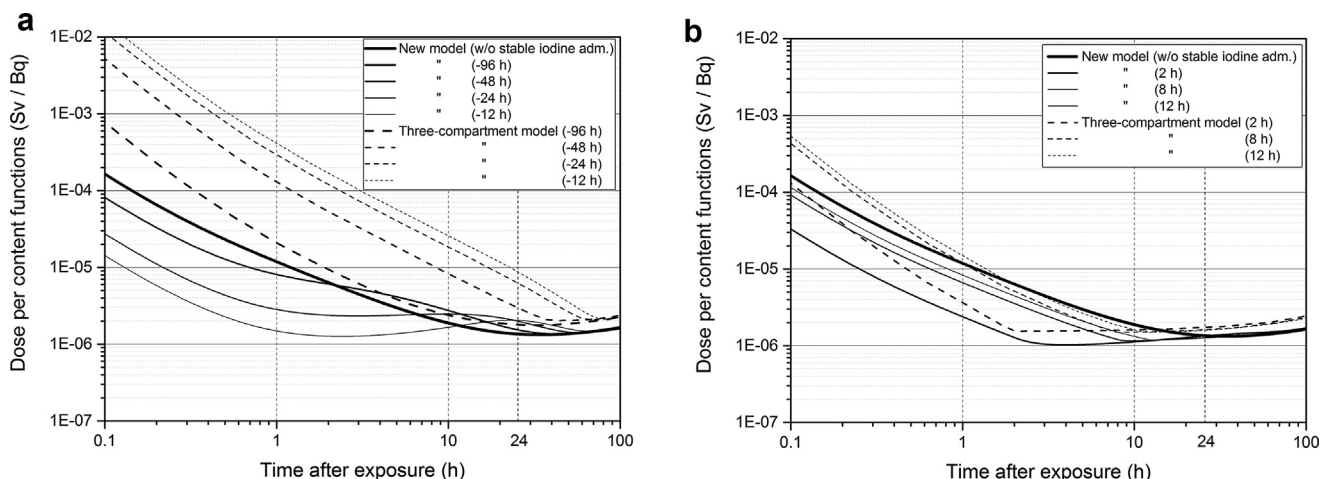
When the protective effects were compared with those reported in previous simulation studies that used the three-compartment biokinetic model, it was found that the new model produced generally lower protective effects than the previous model. The first cause of those differences was the difference in the implementation of thyroid blocking in biokinetic models, as described in the



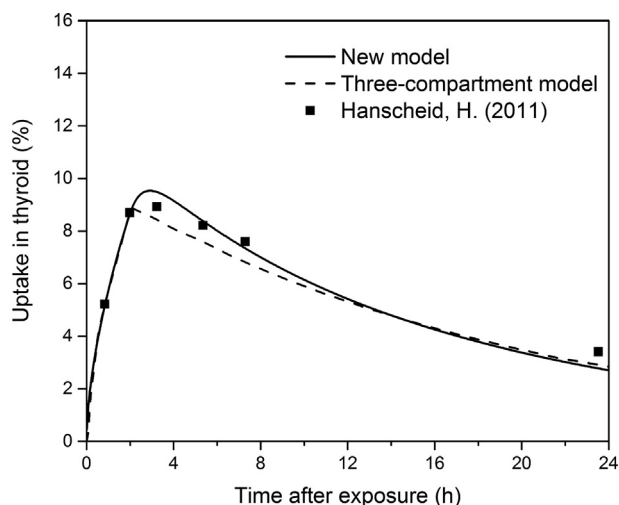
**Fig. 8.** Thyroid equivalent dose coefficients according to stable iodine administration time for inhalation of I-131 particulates with absorption type F. The dose coefficients for the three-compartment model were graphically extracted from the paper of Broggio et al. [7].

previous section. In the new model that was used in this study, further thyroid uptake of iodine inevitably occurs, even if the thyroid is appropriately blocked, because the Blood-to-Thyroid 1 rate is not influenced by thyroid blocking. As shown in Fig. 10, the new biokinetic model still elevates the thyroidal iodine uptake after stable iodine administration (at 2 h after exposure), whereas the three-compartment model immediately prohibits thyroid uptake. This further thyroid uptake, which was obviously observed in the human-based experiment (dots) [23], consequently led to lower protective effects. Another cause of the lower protective effects was presumed to be the difference shown in the calculations of the serum iodide concentrations. The apparent separation of the blood compartment from those with other extrathyroidal iodine might lead to the derivation of much lower and thus more practical serum iodide concentrations than those calculated by previous models. The exponential term of eq. (2) resulted in the faster recovery of Thyroid 1-to-Thyroid 2 rate in lower serum iodide concentration, and thus, the lower protective effect in this study. Nevertheless, it should be noted that the results calculated using the three-compartment model demonstrated differences among themselves. For instance, in the range of 72 h before exposure depicted in Fig. 5, the protective effects reported by Broggio (2019) are seen to be lower than the results calculated in this study using the new biokinetic model; however, the other results are higher than those of this study. Unfortunately, the exact reason was not understood as those studies had not fully explained the biokinetic model calculations.

Although the excessively reduced protective effects when KI was administered before 72–96 h of exposure led to some issues that should be improved, the lower protective effects than those in previous studies correspond well with the results of the model developer [7]. In the paper of the developer, it was observed that the dose coefficients for thyroid blocking based on the new model were substantially higher than those in ICRP publication 53 [24]. In particular, the comparison results that highly correspond to well-controlled experimental data (Fig. 6) indicate that the more practical and accurate thyroid dose assessment can be achieved by adopting the new biokinetic model. In contrast, the three-compartment model derived significantly higher values than did the experimental data. Although the re-evaluated protective effects were a little lower than those observed in previous studies, they still support the validity of the WHO recommendation. The



**Fig. 9.** Thyroid dose per content functions (DPCFs) according to stable iodine administration time for inhalation of I-131 particulates with absorption type F (for administration prior to (a), or after (b) radioiodine exposure).



**Fig. 10.** Uptake in thyroid with thyroid blocking (100 mg potassium iodide administration at 2 h after radioiodine intake). The solid line (this study) and dash line represent the expected uptake functions that were calculated using the new biokinetic model and the three-compartment model, respectively. The dots indicate the further uptakes that were observed in the human experiment.

recommended administrations of 100 mg stable iodine within a period less than 24 h before and up to 2 h after the expected onset of exposure correspond to 86.5% and 76.3% protective effects, respectively.

Even if the protective effect of stable iodine administration is predictable, the appropriate thyroid dose estimation remains a critical issue for triage and subsequent decision-making regarding medical actions. The dosimetric data that were highly dependent on the administration time imply that the dose estimation for thyroid blocking should consider the appropriate dosimetric data corresponding the administration time (Figs. 7–9). However, a great attention should be paid to which biokinetic model is used to derive the dosimetric data because the use of different models can produce greatly different dosimetric data. In particular, Fig. 7 (a) and (b) shows a critical limitation of three-compartment model in producing thyroid retention functions. Not only did the three-compartment model generate thyroid retention functions that start at extremely different points, it also showed unrealistically excessive difference between the retention functions of  $-0.25$  h

( $-15$  m) and 0.25 h (15 m) administrations (e.g., more than 3000-fold difference at 0.1 h after exposure). Although the administration timing ‘before’ or ‘after’ exposure is critical, thyroid retention functions for administration before and after exposure should be similar as administration times draw nearer to exposure. This limitation of the three-compartment model also arises from the direct inhibition of thyroid uptake. In addition, the use of dosimetric data in the three-compartment model can yield a considerably higher thyroid dose estimate in the early phase after exposure than when the data in the new model is used (Fig. 9(a)). As noted in the results section, KI administration at 12 h before exposure and dose assessment within 10 h after exposure can result in a 100-fold difference in thyroid dose estimates depending on the model used. These results indicate that it is imperative to consider the new model in cases needing rapid dose assessment ( $\sim 10$  h after exposure) with KI administration within 24 h before exposure, in accordance with WHO recommendations. Therefore, the use of dosimetric data provided in current study is expected to substantially improve the accuracy of thyroid dose estimation. Furthermore, DPCFs calculated in this study allow more practical application. All DPCFs converged with 25% deviation after 1 d of radioiodine exposure regardless of administration time. In other words, after 1 d of the exposure, the data for unblocked (normal) thyroid can be used without considering the KI administration with an expected uncertainty of 25%; for instance, the dosimetric data provided in ICRP publication 137 and those to be published in environmental intakes of radionuclide (EIR) reports in the future may be used for workers and the public, respectively. With respect to the practical aspects, therefore, we recommend thyroid measurement and dose assessment 1 d after radioiodine exposure to reduce the uncertainty that arises from unclear KI administration time, considering the stabilities of the thyroid retention and DPCF. In addition, 1 d after exposure is also an appropriate timing in terms of thyroid measurement. Within 1 d after exposure, extra-thyroidal radioiodine distributed in the whole body other than thyroid can impact thyroid measurement. Since almost all the radioiodine is accumulated in the thyroid after approximately 1 d of exposure, thyroid measurement thereafter can also improve the accuracy of the results. Nevertheless, when the thyroid dose needs to be assessed rapidly in the early phase or when the accuracy of the thyroid dose needs to be improved, the appropriate data that correspond to administration time should be considered with well-collimated thyroid measurement devices.

## 5. Conclusion

In the current study, the new biokinetic model for iodine, which has been recently adopted as a reference model by the ICRP was analyzed and calculated, for implementing the iodine thyroid blocking. This study provides new and promising information on thyroid dose estimation after thyroid blocking. There remain, however, incomplete aspects of thyroid blocking simulation in the biokinetic model and comparison with human-based data that remain to be investigated. Although the calculated protective effects demonstrated in this study were approximately or precisely compared with available experimental data, quantification of the differences between calculation and experiments is not feasible. Human-based experiments with fixed KI amounts at different administration times will be needed in future to improve reliability. In addition, even if the new biokinetic model was more realistic and was applied in ICRP references, the results of this study reveal that the inhibition of organification is insufficient to fully account for the prolonged efficacy of KI administration. Accordingly, it remains necessary to investigate experimentally and establish thyroid prophylaxis in a biokinetic manner. Moreover, thyroid blocking for other age groups and dietary iodine-rich groups, whose iodine biokinetics could significantly differ from that in the reference biokinetic model, should be investigated in further research.

## Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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