Determination of the Radiation Dose From Administered Apolipoprotein Tracers in Humans

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Radioactive tracers are routinely used in investigation of the metabolism of apolipoprotein kinetics. Here, metabolic studies of apolipoprotein tracers labeled with radioiodine were analyzed to determine the absorbed radiation dose received by the subject. This analysis used compartmental modeling techniques to evaluate the radiation dose to various organs and the total body resulting from radioiodinated tracer injection. In this approach, we combined the published kinetic models of iodine and those of specific apolipoproteins. From the solution of the integrated compartmental models, residence times of the radiation in various source organs, in particular the thyroid, whole body, bladder, and red bone marrow, have been determined for the apolipoproteins apoA-I, apoA-II, very-low-density lipoprotein (VLDL)-apoB, and low-density lipoprotein (LDL)-apoB, each labeled with iodine 123, 133, 124, 131, 126, and 125. These tabulated values were used to calculate radiation doses to the different target organs. The thyroid is the organ that receives the largest dose of delivered radiation, and the importance of the duration of administration of iodine salts in blocking radiation to the thyroid is demonstrated. Optimal block times of 28 days for ^{131}I and 42 days for ^{125}I-labeled apolipoprotein tracers are proposed. When such a protocol is followed, the radiation dose to the thyroid and other organs is small by comparison to radiation doses allowed for workers whose occupation exposes them to radiation. The importance of frequent voiding to reduce the radiation dose to the bladder has also been demonstrated.

INTEREST IN UNDERSTANDING the physiology of lipoprotein particles has led to many studies using both endogenous and exogenous tracers. Since the constituents of a lipoprotein particle can undergo metabolic transitions independently,[1] it is useful to refer to the lipoprotein kinetics with reference to a constituent with which it can be identified. Apolipoproteins A-I (apoA-I) and A-II (apoA-II) are the major protein moieties of human high-density lipoprotein (HDL), comprising approximately 90% of the total HDL protein mass, and may be deemed markers for HDL kinetics. In the case of very–low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), the kinetics of apoB are normally studied. Here, we report dosimetric calculations for these apolipoproteins when labeled with various radionuclides of iodine.

MATERIALS AND METHODS

Theory

The theoretical basis of absorbed dose calculations for tracer kinetics has been developed by Berman[2] and Loevinger et al[3] and is given in MIRD Pamphlet No. 12 and the MIRD Primer. A simplified review of the theory is provided here to aid in following the methodology presented in this report. After a radioactive substance is administered, the activity accumulates in various locations within the body that become the source organs from which radiation is emitted to target organs. The target organs are the numerous sites, including the source organ itself, that absorb radiation, and the absorbed dose (D) is the energy absorbed from ionizing radiation by a target organ. In most biological systems, a substance that initially localizes in one organ is metabolized and distributes to other sites. This, plus the spontaneous process of nuclear transition, gives rise to a finite lifetime of radioactivity within a source organ, ie, the residence time of the radiation ($\tau(\lambda)$). The cumulated activity ($\tilde{A}$) is the sum of nuclear transitions occurring during the time the nuclide resides in the source organ.*

If Δ_i is the mean energy emitted per nuclear transition and Φ is the specific fraction of energy absorbed by a target organ r_k from particles emitted in source organ r_h, we can define a quantity S as the dose absorbed by the target per unit cumulated activity in the source as

$$S(r_k \leftarrow r_h) = \Delta\Phi(r_k \leftarrow r_h) \text{ rad}/\mu\text{Ci h.} \quad (1)$$

The mean absorbed dose to the region k from a source in region h having cumulative activity $\tilde{A}_h$ is given by

$$\overline{D}(r_k) = \tilde{A}\, S(r_k \leftarrow r_h) \text{ rad.} \quad (2)$$

Tables of S values for various radionuclides are given in MIRD Pamphlet No. 11,[4] listing for each radionuclide the absorbed dose in rad/μCi h per unit cumulated activity for various source and target organs.

To calculate the radiation dose to the target organs from each source organ, a knowledge of the cumulated activity in each source organ is necessary. The cumulated activity in region h is the product of the

*As used in this report, residence time has two meanings. In the mathematical compartmental modeling of physiologic systems, it refers to the time a material spends in a compartment or a system of compartments that depict the physiologic pools within which the tracer resides. Alternately, and as used in the present context, it refers to the average time a radionuclide is present and emits radiation within a source organ. When used in this sense, it is a function of both the time the radionuclide resides within the physiologic compartment and the half-life for decay of the radionuclide, and $\tau(\lambda)$ equals $\tilde{A}/A_0$, where A_0 is the amount of activity administered to the subject. Thus, for a unit dose of administered activity, the cumulated activity equals the residence time of the radiation and has the units of time. For clarity, when used in this latter context, it will be referred to as the residence time of radiation to distinguish it from the physiologic residence time.

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residence time of radiation in that region and the administered activity, ie,

$$\tilde{A} = \tau_h(\lambda)\, A_0\ \mu\text{Cih}, \qquad (3)$$

where $\tau_h(\lambda)$ is the residence time (τ) of the radionuclide in the source organ, taking into account the physical decay of the radionuclide (ie, as a function of its decay constant, λ), and A_0 is the total administered activity in μCi.

For a linear, constant parameter system, every administered particle has a priori the same expected residence time in a region (an organ or tissue) regardless of when it enters the system.[2] The residence time of the radiation is thus independent of the total administered activity or the time course of administration and is a continuous function of λ, the physical decay constant of the radionuclide. Therefore, a plot of the residence time versus the physical half-life serves as a universal curve for substances having similar distribution functions, $q_h(t)$, but labeled with different radionuclides, and from this function the cumulated activity in each source organ of interest can be obtained. The distribution function is the activity in a source organ corrected for radioactive decay, for instance, to the time of injection, and the fractional distribution function is the ratio of the distribution function divided by the activity (A_0) in the administered bolus, thus providing a measure of the biological distribution of the activity among the source organs of the body. Thus, the distribution function will be the same for radioiodinated apoA-I tracers irrespective of the iodine nuclide that is used for labeling, and the fractional distribution function (F) describes the ratio of the distribution of activity among the various source organs. For radioiodinated apolipoproteins, these organs are plasma, thyroid, bladder, and red bone marrow. Thus, the dose equivalent (H) of radiation to a target organ from a source organ to a target organ is calculated by the following equation:

$$H = A_0 F \tau(\lambda) SQ \text{ rem}. \qquad (4)$$

The quality factor (Q) for conversion from rad to rem for β and γ radiation being unity, this equation also gives the dose equivalent in rem to the target organ.

In this investigation, published metabolic models of apoA-I,[5] apoA-II,[5] VLDL-apoB,[6] and LDL-apoB[7] have each been combined with a model of iodine kinetics[2] (Figs 1 to 5) to enable calculation of the radiation dose delivered to the various organs by an injected radiolabeled apoprotein. In Figs 8 to 11, plots of the residence time of the radiation for the different apolipoproteins are illustrated, and values obtained for the residence time of radiation in the different source organs for the six iodine isotopes are listed in Tables 1 and 2. Tables 3 and 4 tabulate the dose-equivalent of radiation to various target organs resulting from administration of apolipoproteins labeled with ^{123}I or ^{131}I. Detailed discussion of the figures and tables is presented in subsequent sections.

Iodine Model

The four-compartment model of iodine kinetics in normal subjects reported in MIRD Pamphlet No. 12 was used in our calculations.[2] The model is shown in Fig 1. Compartments 1 to 4 represent extrathyroidal iodide, thyroidal iodide (mostly in organic form), and extrathyroidal triiodothyronine (T_3) and thyroxine (T_4), respectively. Plasma iodide is included in compartment 1, and the iodide released from protein deionization enters this pool, which is also the source for urinary iodine excretion. By combining each of the apolipoprotein models with the iodine kinetic model, the metabolism of the radioiodine ligand of the apolipoprotein tracer can be traced until eliminated from the body. A brief discussion of each of the published apolipoprotein models and their integration with the iodine model follows.

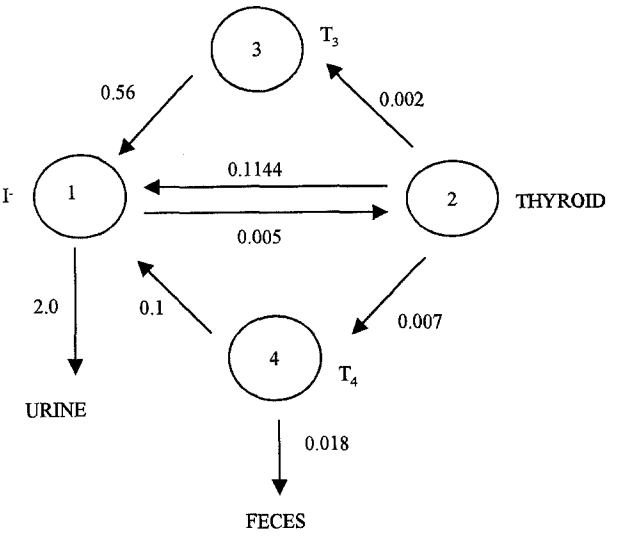

Fig 1. Compartmental model of iodine kinetics. The Berman model of iodine kinetics was used in these calculations.[2] Fractional exchange coefficients are in days.

ApoA Models

Zech et al[5] developed a model for the metabolism of apoA-I and apoA-II in humans based on a kinetic study of 20 normal subjects injected with radioiodinated (^{131}I and ^{125}I) apoA-I and apoA-II. In their study, subjects received a weight-maintenance diet and potassium iodide was given to minimize radioiodine uptake by the thyroid. Following injection of radioiodinated apolipoproteins, fasting plasma samples were collected for 14 days. Plasma, urine, and whole-body radioactivity were determined. The apoA-I model consists of two plasma compartments, one of which exchanges with two nonplasma compartments. ApoA-I catabolism occurs solely from the two plasma pools, and apoA-I has a residence time of 5.04 days. The apoA-II model, on the other hand, has a single plasma compartment exchanging with two nonplasma compartments, and apoA-II catabolism occurs by pathways from both the plasma and one of the extravascular compartments. ApoA-II has a residence time of 5.5 days.

The integrated model for apoA-I is shown in Fig 2. In this model, the output from the two apoA-I plasma compartments, which reflects the catabolism of these proteins with the liberation of iodine, enters the extrathyroidal iodide pool represented by compartment I, which is synonymous with compartment I in the iodide model. Thus, the two models may be merged. Accordingly, the integrated model represents the kinetics of the radioiodine ligand of apoA-I and may be used for dosimetric studies of this apolipoprotein tracer. A similar strategy has been adopted for each apolipoprotein. The integrated model for apoA-II is shown in Fig 3.

VLDL-ApoB Model

ApoB is metabolized through several pathways, and the leucine tracer, biosynthetically incorporated into plasma apoB, permits distinguishing the separate pathways by which the metabolism of apoB is channeled[6] (Fig 4). Using a ^{3}H-leucine tracer, Fisher et al[6] conclude that apoB is secreted (a) as large VLDL metabolized by a delipidation chain, (b) as a VLDL fraction that is rapidly converted to IDL, and (c) as IDL. ApoB appears to be metabolized along two pathways, through the delipidation pathway from large VLDL to small VLDL, IDL, and LDL, and alternately as nascent VLDL and IDL particles rapidly metabolized to LDL. Both pathways feed large and small LDL subspecies, with the larger LDL being sequentially converted to the smaller species. ApoB may be catabolized at several points along these pathways, and radioiodine from the degraded apoB, which enters the iodide pool,

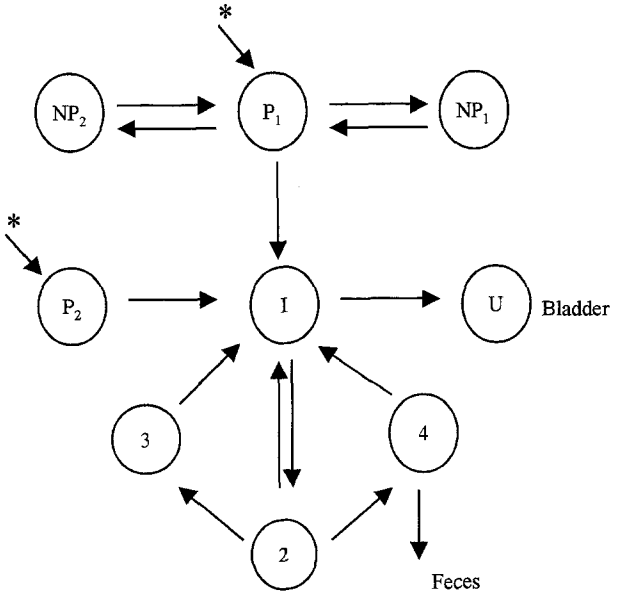

Fig 2. Integrated model for iodine-labeled ApoA-I. The integrated model for evaluating iodinated apoA-I dosimetry combines the iodine model of Fig 1 with the kinetic model for the metabolism of apoA-I in humans developed by Zech et al.[5] P1 and P2 are, respectively, slow and rapid turnover apoA-I plasma compartments, and P1 is in equilibrium with 2 nonvascular exchange compartments, NP1 and NP2. Upon deiodination of apoA-I, the inorganic iodine enters the extrathyroidal iodine pool, I, which provides the common link between the apoA-I and iodine models.

permits this model to be integrated with the iodine compartmental model (Fig 4). This kinetic model for VLDL-apoB was used to determine the residence times in source organs, and the calculations for radiation dose used fractional rate coefficients reported for normal subjects.

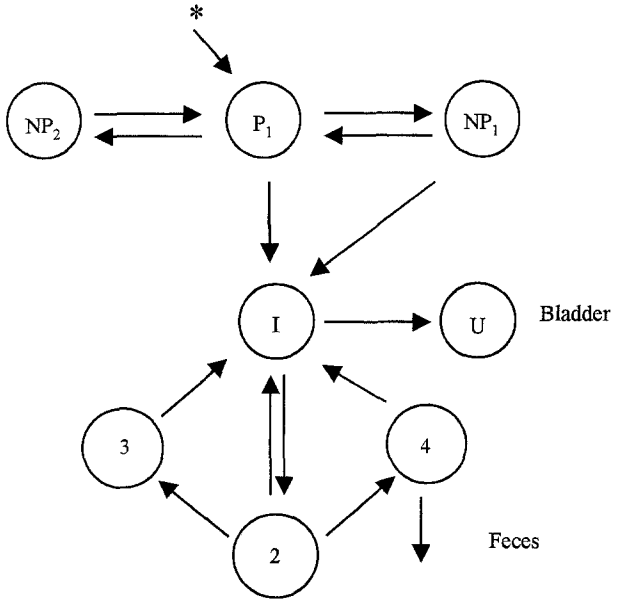

Fig 3. Integrated model for iodine-labeled ApoA-II. This model traces the metabolism of administered radioiodinated apoA-II. The apoA-II model is from Zech et al.[5] A single plasma compartment, P1, exchanges with 2 extraplasma compartments, and 2 catabolic pathways, as shown, link this model to the extravascular pool of the iodine model.

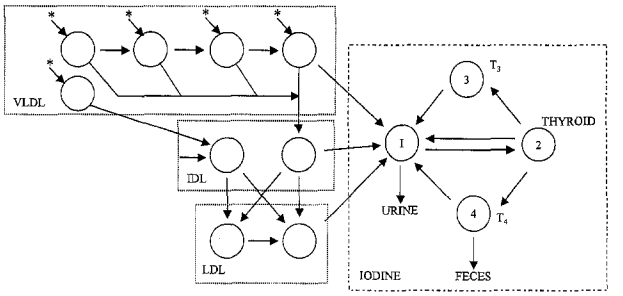

Fig 4. Integrated model for iodine-labeled VLDL-ApoB. This integrated model links the VLDL-ApoB model of Fisher et al[6] with the iodine kinetic model.

Since the full VLDL-apoB model was developed based on a [^{3}H]leucine tracer,[6] only the part of the model dealing with the metabolism of apoB subsequent to its secretion into plasma was used for dosimetric purposes. The plasma mass of VLDL-apoB was measured; however, the distribution of mass among the pools in VLDL was calculated from the model, and the initial distribution of iodine tracer was then divided among these VLDL compartments based on a ratio of their calculated masses. There are no recognized extravascular compartments that exchange with plasma VLDL or IDL, and the extravascular exchange of LDL-apoB is poorly determined with the leucine tracer and is omitted in this model that is used for dosimetric calculations of a VLDL-apoB tracer.

LDL Model

The LDL model of Goebel et al was chosen for the purposes of this study.[7] This is analogous to model B proposed by Foster et al.[8] The Goebel model is based on data from 25 single-injection studies on a variety of patients. It analyzes the kinetics of radioiodine-labeled LDL in plasma using a three-compartment model for labeled LDL-apoB kinetics that has two plasma compartments, one of which exchanges with a nonplasma compartment. Figure 5 shows that the output from compartments 1 and 2 was fed to the extrathyroidal iodine compartment upon integration of the iodine kinetic model with the LDL kinetic model.

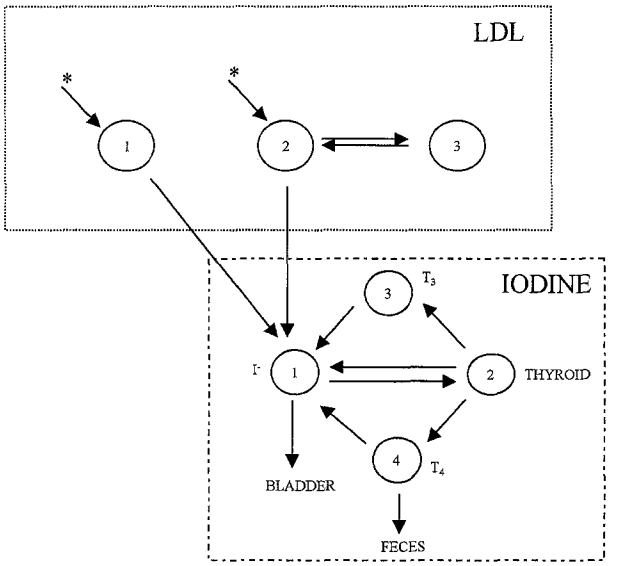

Fig 5. Integrated model for iodine-labeled LDL-ApoB. The LDL-ApoB model of Goebel et al and Foster et al[7,8] is integrated with the iodine kinetic model as described in the text.

Integration of the Iodine Model and the Apolipoprotein Model

The following assumptions have been made in the actual implementation of the integrated models to obtain the values for cumulated activity in the source organs.

1. The activity of the administered radiolabeled substance is sufficiently low that no structural damage to the protein occurs that might interfere with its kinetics.
2. The tracee is in steady state, and thus the tracer introduced into the biological system follows linear kinetics with time-invariant parameters.
3. For purposes of dose computation, whole-body, thyroid, bladder, and red bone marrow are considered the source organs of interest that contribute to the doses in the 20 target organs listed in MIRD 11.[4] The fractional distribution functions for the thyroid, bladder, plasma, and red bone marrow were, respectively, 1, 1, 0.92, and 0.08. For each apolipoprotein, the whole body is considered to consist of all of the compartments in the integrated apolipoprotein-iodine model.
4. The iodine isotopes are assumed to be 100% pure. The fractional uptake of iodine by the thyroid is reduced to zero through dilution by administration of a saturating dose of potassium iodide. When administration of KI, is discontinued, the fractional uptake of iodine by the thyroid increases linearly and reaches values of 0.1 pools per day over a 10-day period.

Compartmental analysis was used to analyze the effective clearance of the radionuclide from each of the source organs as a function of time, and graphs to compute the cumulated activity of the radionuclide were obtained as described by Berman.[2] The compartmental modeling and analysis was performed using the SAAM/CONSAM computer program.[9] For purposes of generalizing the graphical results to any isotope of the user's choice, the physical half-life of the radionuclides from 0.1 to 10,000 days was calculated, but the data shown in Figs 8 to 11 have been truncated at 300 days. Radioiodine block times to the thyroid were determined at 14-day intervals up to 56 days.

RESULTS AND DISCUSSION

Calculation of the Radiation Dose

The iodinated plasma apoA-I and urine radioactivity data were analyzed using the integrated iodine–apoA-I model shown in Fig 2. The integrated models for apoA-II, VLDL-apoB, and LDL-apoB are shown in Figs 3, 4, and 5, respectively. The simulated plot of the plasma activity and fractional urine activity for iodinated apoA-I is shown in Figs 6 and 7,

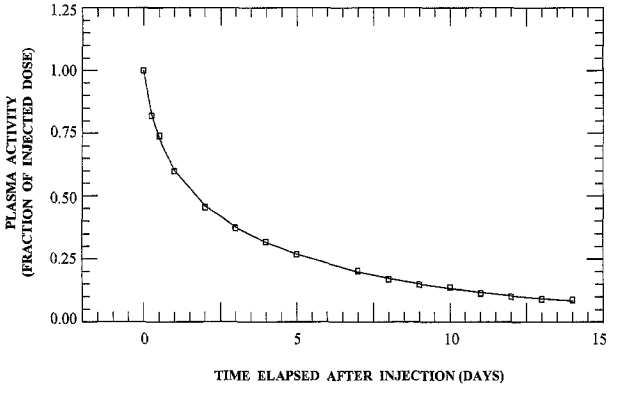

Fig 6. ApoA-I plasma activity. Tracer activity in plasma after injection of iodine-labeled apoA-I. The curve was obtained through solution of the integrated model.

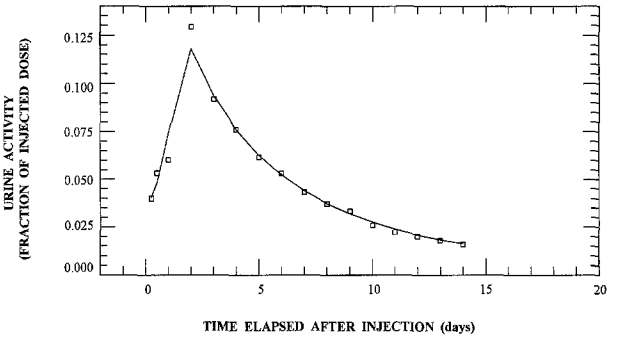

Fig 7. ApoA-I fractional urine activity. Fractional urine activity for a radioiodine-labeled apoA-I injected into the subject. The plot is obtained by solution of the integrated model with each point denoting the recovered activity in urine for 1 day.

respectively. Similar plots (not shown) were obtained for the other apolipoproteins.

The plots of the residence times of radiation in the whole body and source organs, as a function of the half-life of the radioactive decay of the iodine nuclide, are presented in Figs 8 to 11 for apoA-I, apoA-II, VLDL-apoB, and LDL-apoB, respectively. These figures also demonstrate the effect of varying the duration of thyroid blockade with potassium iodide. Tables 1 and 2 present a tabulation of these calculated residence times, taken from the graphs, in the various source organs for the four apolipoproteins, each labeled with six different iodine isotopes. The effect of the varying iodine block periods of 1, 14,

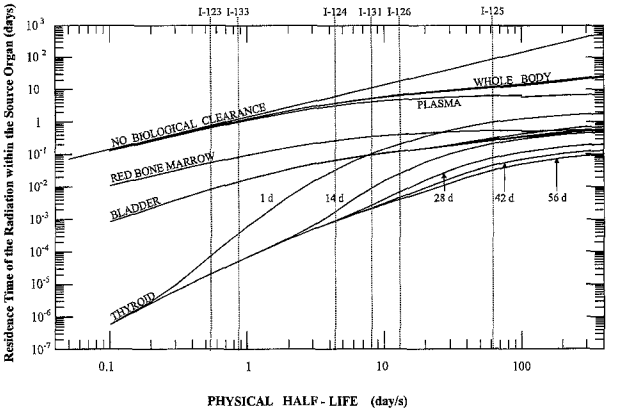

Fig 8. Residence time of the radiation for ApoA-I. For Fig 8 to 11, simulated plots show the residence times for each of the compartments chosen as source organs as a function of the half-life of the radionuclides of iodine. The vertical dotted lines cut the abscissa at the physical half-lives of the isotopes, as indicated. To obtain the residence time for a particular isotope and source organ, read the value on the ordinate at which the chosen dotted line cuts the curve of the particular source organ. The top linear plot depicts the residence time of radiation of an administered tracer if no biological clearance occurred, ie, if the physiological residence time was infinite. The plots demonstrate the effect of increasing the iodine block time in 2-week increments beginning with a 1-day iodine blockade of the thyroid. The effects are clearly evident for the thyroid compartment, and 5 distinct curves are resolved. As shown here and tabulated in Tables 1 and 2, administration of iodine shows minimal (whole-body and bladder) to no effect on the residence time of radiation of the other source organs.

Table 1. ApoA-I: Residence Time of the Source Organs (days)

		^{123}I	^{133}I	^{124}I	^{131}I	^{126}I	^{125}I
Half-life (d)		5.418E−01	8.667E−01	4.208E+00	8.042E+00	1.300E+01	6.042E+01
Source Organ	Thyroid Block						
Thyroid	1 d	9.77E−05	4.52E−04	2.73E−02	8.97E−02	1.85E−01	8.49E−01
	14 d	3.04E−05	7.43E−05	1.64E−03	9.25E−03	2.80E−02	2.40E−01
	28 d	3.04E−05	7.43E−05	1.02E−03	3.23E−03	9.07E−03	1.04E−01
	42 d	3.04E−05	7.43E−05	9.96E−04	2.48E−03	5.31E−03	5.43E−02
	56 d	3.04E−05	7.43E−05	9.95E−04	2.37E−03	4.40E−03	3.27E−02
Total body	1 d	7.01E−01	1.06E+00	3.40E+00	4.90E+00	6.14E+00	9.99E+00
	56 d	7.01E−01	1.06E+00	3.37E+00	4.81E+00	5.95E+00	9.08E+00
Plasma	1 d	5.53E−01	7.92E−01	2.11E+00	2.79E+00	3.27E+00	4.39E+00
	56 d	5.53E−01	7.92E−01	2.11E+00	2.79E+00	3.27E+00	4.39E+00
Red bone marrow	1 d	4.59E−02	6.57E−02	1.75E−01	2.31E−01	2.72E−01	3.64E−01
	56 d	4.59E−02	6.57E−02	1.75E−01	2.31E−01	2.72E−01	3.64E−01
Bladder	1 d	1.14E−02	1.97E−02	7.14E−02	1.01E−01	1.27E−01	3.01E−01
	56 d	1.14E−02	1.97E−02	7.23E−02	1.03E−01	1.28E−01	2.59E−01

NOTE. Values were extracted from respective SAAM output. These values can also be read from the respective graphs in Fig 8.

28, 42, and 56 days on the residence time of a radioiodinated apoA-I tracer in the source organs is demonstrated in Table 1.

Figure 8 and Table 1 demonstrate several important points. With regard to the thyroid gland, for ^{123}I, a nuclide with a half-life of only 0.541 days, thyroid blockade extending over 56 days has little effect on the residence time of radiation in this gland; however, for the longer-lived isotopes, blockade of the thyroid gland becomes increasingly important to reduce the radiation trapped within the gland, as seen for ^{131}I and particularly ^{125}I. By contrast, for the other source organs, thyroid blockade has minimal to indeterminable effect. Figures 9 to 11 are a graphical presentation for the other three apolipoproteins, and the findings are similar to those for apoA-I. Inspection of these data with respect to iodine blockade of the thyroid gland demonstrates that the residence time of radiation in the thyroid in the case of ^{131}I approaches a minimum at 28 days of blockade, and for ^{125}I at 42 days. Accordingly, for the other three apolipoproteins, the tabulated values presented in Table 2 for the residence time of radiation in the thyroid and total body are only provided for 28 and 42 days of thyroid blockade. For human radioiodine tracer studies, thyroid blockade is required, and as will be discussed subsequently, these two block times are of particular importance. For the other source organs, only single values for residence time are provided, since, as shown in the figures and Table 1, these values are independent of thyroid blockade.

Multiplying the value for the residence time of radiation within the body by the total administered activity gives the cumulated activity for the whole body. For the source organs, the total administered activity must be multiplied by the fractional distribution factor and then the residence time in calculating the cumulated activity. The values from Tables 1 and 2 and the S values corresponding to the isotope and organ of interest from the MIRD 11 tables[4] were used with Eq 4 to calculate the dose-equivalent radiation (H) from each of these source organs to the 20 target organs. Examples of this calculation are given in the appendix to illustrate computation of the dose from a dual iodine tracer.

Table 3 presents these calculated doses of radiation delivered to each of 19 target organs when the whole body is considered the source. Tabulated values are presented for each of the four apolipoproteins labeled with either ^{131}I or ^{125}I, the two iodine nuclides commonly used as tracers in lipoprotein metabolic studies, assuming 28 or 42 days of thyroid blockade. Inspection of these data shows consistency for the dose of radiation delivered to each of the target organs for any given apolipoprotein tracer.

Table 4 presents similarly calculated values, but with the

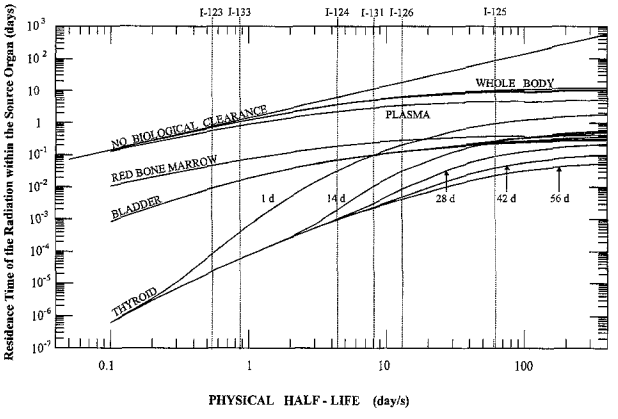

Fig 9. Residence time of the radiation for ApoA-II.

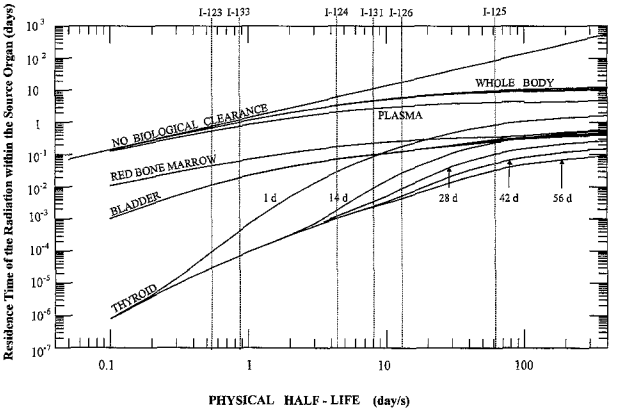

Fig 10. Residence time of the radiation for VLDL-ApoB.

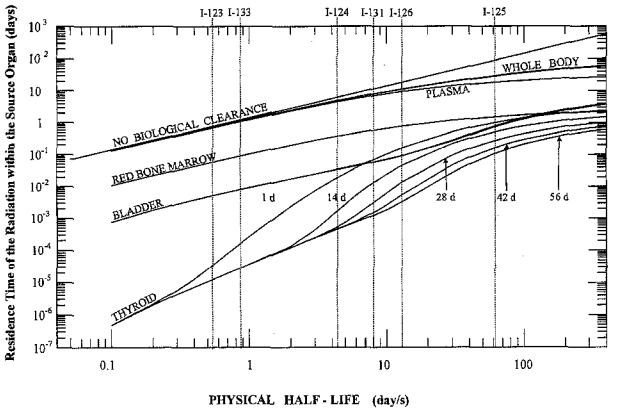

Fig 11. Residence time of the radiation for LDL-ApoB.

thyroid gland as the source organ, and only three target organs are reported. For apoA-I, values for the block time extending from 1 to 56 days clearly demonstrate the importance of blocking radioiodine uptake by the thyroid, since an order of magnitude decrease in dose to the thyroid with ^{131}I occurs by extending the duration of the thyroid block from 1 day to 2 weeks, gradually leveling off after 28 days. A similar effect is seen with ^{125}I, but 42 days of block time are required to ameliorate the dose to the thyroid with this nuclide. Thus, for these two radionuclides commonly used in apolipoprotein tracers, the dose-equivalent radiation to the thyroid is in the range of 40 to 60 mrem/μCi for a 1-day iodine block (Table 4). When this value is multiplied by an injected activity of 25 to 100 μCi, the radiation delivered to the thyroid is substantial (see examples in the appendix). When a dual-tracer study using ^{131}I and ^{125}I is performed, the effect on the radiation dose is cumulative. These data most clearly establish the importance of the 28- and 42-day block times when using ^{131}I and ^{125}I tracers, respectively.

By contrast, for all of the 18 other target organs, the radiation dose received when the thyroid is the source organ is very low. Since radioiodine is excreted in the urine, values for the bladder wall and also those for the total body are included in this table as examples of the low level of radiation delivered to organs other than the thyroid. Even though the doses to the bladder and total body are very small, one does see an effect with an increased thyroid block time. The findings with apoA-II and the two apoB tracers are similar; therefore, in Table 4 we record only the dosages delivered at 28 and 42 days.

Model Dependency of the Dosimetry

The assumptions inherent in each of the kinetic models and the accuracy of these models in correctly representing the physiology place limitations on the results of calculations performed in this study. However, these models constitute our current quantitative understanding of apolipoprotein and iodine metabolism, and as such provide the best current dosimetry estimations. That these estimations are model-dependent is illustrated by the following example. The residence times of radiation for the radioiodine-labeled tracers of apoA-I, apoA-II, and VLDL-apoB, which includes the IDL and LDL by-products, are of a similar magnitude for a specific nuclide (Tables 1 and 2), reflecting the similarity in the times that these apolipoproteins and their by-products reside within the body.

Table 2. Residence Time of the Source Organs (days)

Isotope		^{123}I	^{133}I	^{124}I	^{131}I	^{126}I	^{125}I
Half-life (d)		5.418E−01	8.667E−01	4.208E+00	8.042E+00	1.300E+01	6.042E+01
Source Organ	Thyroid Block						
ApoA-II							
Total body	28 d	7.17E−01	1.09E+00	3.61E+00	5.15E+00	6.33E+00	9.19E+00
	42 d	7.17E−01	1.09E+00	3.61E+00	5.15E+00	6.32E+00	9.13E+00
Thyroid	28 d	2.38E−05	5.97E−05	9.35E−04	3.11E−03	8.70E−03	8.92E−02
	42 d	2.38E−05	5.97E−05	9.09E−04	2.34E−03	4.86E−03	3.94E−02
Plasma	28 d	5.64E−01	8.12E−01	2.23E+00	2.98E+00	3.52E+00	4.68E+00
Red bone marrow	28 d	4.68E−02	6.74E−02	1.85E−01	2.48E−01	2.92E−01	3.88E−01
Bladder	28 d	9.21E−03	1.63E−02	6.77E−02	1.01E−01	1.29E−01	2.31E−01
VLDL-ApoB							
Total body	28 d	7.21E−01	1.10E+00	3.73E+00	5.37E+00	6.67E+00	1.08E+01
	42 d	7.21E−01	1.10E+00	3.73E+00	5.37E+00	6.67E+00	1.08E+01
Thyroid	28 d	2.09E−05	5.24E−05	8.69E−04	2.77E−03	7.48E−03	9.17E−02
	42 d	2.09E−05	5.24E−05	8.51E−04	2.25E−03	4.84E−03	5.70E−02
Plasma	28 d	6.63E−01	1.01E+00	3.15E+00	4.27E+00	5.01E+00	6.44E+00
Red bone marrow	28 d	5.50E−02	8.35E−02	2.62E−01	3.55E−01	4.16E−01	5.35E−01
Bladder	28 d	8.34E−03	1.46E−02	6.46E−02	9.81E−02	1.26E−01	3.37E−01
LDL-ApoB							
Total body	28 d	7.38E−01	1.15E+00	4.78E+00	7.99E+00	1.13E+01	2.86E+01
	42 d	7.38E−01	1.15E+00	4.78E+00	7.99E+00	1.13E+01	2.84E+01
Thyroid	28 d	1.27E−05	2.89E−05	4.89E−04	3.15E−03	1.38E−02	2.69E−01
	42 d	1.27E−05	2.89E−05	4.36E−04	1.53E−03	5.59E−03	1.59E−01
Plasma	28 d	7.03E−01	1.10E+00	4.42E+00	7.09E+00	9.54E+00	1.83E+01
Red bone marrow	28 d	5.84E−02	9.14E−02	3.67E−01	5.89E−01	7.92E−01	1.52E+00
Bladder	28 d	5.19E−03	8.14E−03	3.36E−02	5.93E−02	9.27E−02	7.44E−01

NOTE. Values are extracted from respective SAAM output. These values can also be read from the respective graphs in Figs 9 to 11.

Table 3. Effect of Varying Thyroid Block Time on the Dose-Equivalent Radiation to Target Organ With Whole Body as Source Organ (mrem/μCi injected)

Target Organ/ Block Time	ApoA-I		Apo-AII		VLDL-ApoB		LDL-ApoB	
	^{131}I	^{125}I	^{131}I	^{125}I	^{131}I	^{125}I	^{131}I	^{125}I
	28 d	42 d	28 d	42 d	28 d	42 d	28 d	42 d
Adrenals	1.27E+00	3.01E−01	1.25E+00	3.01E−01	1.42E+00	3.57E−01	2.11E+00	9.39E−01
Bladder wall	1.16E+00	3.41E−01	1.13E+00	3.42E−01	1.30E+00	4.04E−01	1.93E+00	1.06E+00
Bone (total)	1.06E+00	4.81E−01	1.25E+00	4.82E−01	1.18E+00	5.71E−01	1.76E+00	1.50E+00
GI (stomach wall)	1.16E+00	3.41E−01	1.25E+00	3.42E−01	1.30E+00	4.04E−01	1.93E+00	1.06E+00
GI (small intestine)	1.16E+00	3.61E−01	1.25E+00	3.62E−01	1.30E+00	4.28E−01	1.93E+00	1.13E+00
GI (lower intestine wall)	1.16E+00	3.61E−01	1.25E+00	3.62E−01	1.30E+00	4.28E−01	1.93E+00	1.13E+00
Kidneys	1.16E+00	3.21E−01	1.25E+00	3.21E−01	1.30E+00	3.80E−01	1.93E+00	1.00E+00
Liver	1.16E+00	3.41E−01	1.25E+00	3.42E−01	1.30E+00	4.04E−01	1.93E+00	1.06E+00
Lungs	1.16E+00	3.61E−01	1.25E+00	3.62E−01	1.30E+00	4.28E−01	1.93E+00	1.13E+00
Marrow (red)	1.16E+00	5.21E−01	1.11E+00	5.22E−01	1.30E+00	6.18E−01	1.93E+00	1.63E+00
Other (muscle)	1.04E+00	3.01E−01	1.25E+00	3.01E−01	1.16E+00	3.57E−01	1.72E+00	9.39E−01
Ovaries	1.16E+00	3.41E−01	1.25E+00	3.42E−01	1.30E+00	4.04E−01	1.93E+00	1.06E+00
Pancreas	1.16E+00	3.61E−01	9.41E−01	3.62E−01	1.30E+00	4.28E−01	1.93E+00	1.13E+00
Skin	8.78E−01	2.20E−01	1.25E+00	2.21E−01	9.81E−01	2.62E−01	1.46E+00	6.89E−01
Spleen	1.16E+00	3.61E−01	1.13E+00	3.62E−01	1.30E+00	4.28E−01	1.93E+00	1.13E+00
Testes	1.06E+00	2.81E−01	1.10E+00	2.81E−01	1.18E+00	3.33E−01	1.76E+00	8.76E−01
Thyroid	1.03E+00	3.01E−01	1.25E+00	3.01E−01	1.15E+00	3.57E−01	1.71E+00	9.39E−01
Uterus (nongravid)	1.16E+00	3.41E−01	1.12E+00	3.42E−01	1.30E+00	4.04E−01	1.93E+00	1.06E+00
Total body	1.05E+00	3.41E−01	1.05E+00	3.42E−01	1.17E+00	4.04E−01	1.74E+00	1.06E+00

NOTE. List of target organs taken from MIRD Pamphlet No. 11.[4] Values are extracted from radiation dose tables computed for all 8 iodine-labeled apolipoprotiens, for each block time, and for all source organs in Figs 8 to 11.

However, the cumulative activities for LDL-apoB are consistently higher. It is known that LDL-apoB does exchange with extravascular compartments,[10] even though the kinetics are poorly determined. The LDL-apoB model selected for these dosimetry calculations includes an exchange compartment[7] (Fig 5). When the additional time that LDL-apoB resides within this extravascular exchange compartment is taken into account, the physiologic residence time for LDL-apoB increases substantially as compared with a residence time calculated solely on the basis of the time this lipoprotein resides in plasma (the reciprocal of the fractional catabolic rate). In many LDL kinetic studies, the plasma residence time, which ignores extravascular LDL, is reported. However, for dosimetry calculations, it seemed advisable to include this extravascular pool even though the transfer rate coefficients for the exchange pools are less well determined. On the other hand, in the VLDL-apoB model, neither VLDL nor IDL have exchangeable extravascular pools, and LDL exchange is ignored in those computations. This decision explains the increase in the residence time of the radiation and the radiation dose calculated for this lipoprotein. These observations demonstrate clearly that the dosimetry is model-dependent.

Bladder Voiding Frequency

The effect of bladder voiding frequency on radiation dose to the bladder was also analyzed to determine a protocol that would minimize radiation to the bladder (data not shown). The optimal bladder voiding frequency to minimize the radiation dose to the bladder wall for patients receiving any of the radioiodine isotopes was at least once every 3 hours on the day of tracer administration, every 6 hours until 10 days, and every 12 hours up to 21 days; thereafter, the voiding frequency was a minimum of once daily, and the simulation was extended to 900 days. The major influence on dose occurs in the initial 10-day

Table 4. Effect of Varying Thyroid Block Time on the Dose-Equivalent Radiation to Target Organs With the Thyroid as the Source Organ (mrem/μCi injected)

Apolipoprotein	Block Time (d)	^{131}I			^{125}I		
		Thyroid	Bladder Wall	Total Body	Thyroid	Bladder Wall	Total Body
ApoA-I	1	4.73E+01	4.52E−05	2.04E−02	6.11E+01	7.74E−09	3.26E−02
	14	4.88E+00	4.66E−06	2.11E−03	1.73E+01	2.19E−09	9.21E−03
	28	1.70E+00	1.63E−06	7.36E−04	7.48E+00	9.47E−10	3.99E−03
	42	1.31E+00	1.25E−06	5.66E−04	3.91E+00	4.95E−10	2.09E−03
	56	1.25E+00	1.19E−06	5.41E−04	2.35E+00	2.98E−10	1.25E−03
ApoA-II	28	1.64E+00	1.57E−06	7.09E−04	6.42E+00	8.14E−10	3.43E−03
	42	1.24E+00	1.18E−06	5.34E−04	2.84E+00	3.59E−10	1.51E−03
VLDL-ApoB	28	1.46E+00	1.40E−06	6.32E−04	6.60E+00	8.36E−10	3.52E−03
	42	1.19E+00	1.13E−06	5.12E−04	4.10E+00	5.20E−10	2.19E−03
LDL-ApoB	28	1.66E+00	1.59E−06	7.18E−04	1.94E+01	2.45E−09	1.03E−02
	42	8.06E−01	7.70E−07	3.48E−04	1.15E+01	1.45E−09	6.11E−03

period. With this regimen, the bladder dose was a factor of 2 less than for a regimen of bladder voiding every 6 hours on the first day and once daily thereafter. These observations establish the importance of frequent bladder voiding following tracer administration.

Risk From Radiation Exposure

The primary purpose of these dosimetric calculations is to determine the risk of exposure to radiation for healthy subjects and patients who volunteer as participants in metabolic tracer studies. From this analysis, it is apparent that the choice of the radioiodine isotope liganded to the apolipoprotein is of major significance, as are the physiologic residence times of the apolipoprotein and of the free iodine released upon deiodination of the protein tracer. Figures 8 to 11 clearly demonstrate that radiation to the thyroid gland is very sensitive to iodine blockade, and the data in Table 1 tabulate this effect. Table 4 provides the calculated values for the radiation dose delivered to the thyroid and the reduction in dose that is achieved by administration of a solution of potassium iodide. For ^{131}I-apolipoprotein tracers, the steep decrease in radiation dose resulting from thyroid blockade begins to level off at 28 days, and for ^{125}I-apolipoproteins this occurs at about 42 days. Unquestionably, it is of paramount importance to reduce the radiation exposure to any subject who is a volunteer in a tracer kinetic study. To gain some appreciation of the physiologic significance of the radiation dose to the iodine-blocked thyroid glands of these subjects, one may consult the *Standards for Protection Against Radiation* published by the Nuclear Regulatory Commission. For those whose occupation requires them to be exposed to radiation, the annual limit of exposure to the total body is 5 rem and to the thyroid 50 rem.[11] Table 3 shows that the radiation dose to the total body for a ^{131}I-labeled apolipoprotein with an iodine block period of 28 days is about 1 to 2 mrem/μCi, and thus for injection of 25 μCi of such an ^{131}I tracer, the dose would be 0.02 to 0.05 rem. Similar calculations for the dose to the thyroid gland, again assuming a 28-day thyroid block, yield values of about 2 mrem/μCi and 0.05 rem for a 25-μCi dose (Table 4). For ^{125}I-apolipoprotein tracers administered with a 42-day thyroid block time, the radiation dose to the total body is 0.3 to 1 mrem/μCi or 0.015 to 0.05 rem for a 50-μCi tracer injection, and the radiation dose to the thyroid gland is 4 to 11 mrem/μCi or 0.2 to 0.6 rem for 50 μCi ^{125}I-apolipoprotein.

Conclusion

In this study, we have used knowledge of the metabolism of apolipoproteins gained through tracer kinetic investigations and the resultant compartmental models to provide a quantitative description of these metabolic systems for the purpose of performing dosimetric calculations. Radiation exposure to subjects has been determined when administering radioiodinated tracers for apoA-I, apoA-II, VLDL-apoB, or LDL-apoB. The study also brought into sharp focus the importance of administration of iodine salts to block radioiodine uptake by the thyroid gland, because this organ receives the highest dose of radiation when radioiodinated apolipoprotein tracers are administered. The duration of the thyroid block time is, of course, an arbitrary decision; however, 28 days of potassium iodide administration for ^{131}I-apoprotein tracers and 42 days for ^{125}I-apoproteins appears a rational choice to provide protection to the thyroid gland. Based on data from the Nuclear Regulatory Commission, radiation doses resulting from administration of radioiodinated apolipoprotein tracers are small as compared with radiation exposure permitted for occupational workers; however, minimization of the radiation exposure is an important goal. With this end in sight and recognizing that the excretion of iodide ion occurs via the urinary tract, recommendations for the minimal frequency of bladder voiding have also been proposed based on dosimetry calculations to the bladder.

Finally, it should be remembered that the accuracy of dose computations is model-dependent and assumes the validity of the models. This was clearly seen with regard to the exchange compartments in the LDL-apoB model. The results of this investigation should help researchers in better designing radioiodine-labeled studies of apolipoproteins. As metabolic models for other apolipoproteins are developed, this type of analysis should be applicable for calculating dosimetry.

APPENDIX

This is an example of the calculation of radiation dose to the thyroid gland in a tracer study with radioiodinated apoA-I in which the thyroid was only blocked for 1 day. The target organ is the thyroid, and the source organs are the thyroid, whole body, red bone marrow, and bladder. Three calculations are performed, first assuming a ^{131}I-labeled tracer, second a ^{125}I tracer, and third a dual-tracer study using both ^{131}I and ^{125}I.

Example 1: Dose From 25 μCi ^{131}I

(a) Residence time in thyroid for ^{131}I-apoA-I = 0.0897 days (from Table 1)
Residence time ($\tau(\lambda)$) = 0.0897 · 24 = 2.153 h
Distribution factor (F) = 1
S (thy ↔ thy, ^{131}I) = 0.022 rad/μCi-h (from MIRD Pamphlet 11)
Quality factor (Q) for β, γ, and x-rays = 1
Dose to thyroid from 1 μCi = $A_0 \cdot (\tau(\lambda)) \cdot F \cdot S$ (rad/μCi-h) · Q 1 (rem/rad) (from Eq 4)
Dose = 1 μCi · 0.0897 d · 24 h/d · 1 · 0.022 rad/μCi-h · 1 = 0.0474 rem per μCi
Dose from 25 μCi ^{131}I = 0.0474 · 25 = 1.18 rem
(b) Residence time in whole body = 4.897 d, F = 0.92, S (thy ← wb, ^{131}I) = 9.7 E-06
Dose from whole body to thyroid for 25 μCi = 25 · 4.897 · 24 · 0.92 · 9.7 E-06 · 1 = 26 mrem
The distribution factor for red bone marrow is 0.083 and for bladder 1. The residence times are 0.231 and 0.101 days, respectively. The S factor to thyroid as target organ from source organ rbm is 2.3 E-06 and from bladder 2.1 E-08, respectively. Following the procedure above with these values

(c) Dose to thyroid from red bone marrow = 0.026 mrem
(d) Dose to thyroid from bladder = 1.27 E-03 mrem
Total dose to thyroid from all source organs from 25 μCi ^{131}I = (a + b + c + d) = 1.21 rem

Example 2: Dose From 50 μCi ^{125}I

The residence time in whole body is 9.99 d, thyroid 0.849 d, red bone marrow 0.364 d, and bladder 0.301 d. The corresponding S factors are 1.5 E-06, 3 E-03, 7.3 E-08, and 3.6 E-13. Using the respective distribution factors and the activity administered and following the above procedure,
Dose to thyroid from whole body = 18 mrem
Dose to thyroid from thyroid = 3,060 mrem
Dose to thyroid from rbm = 2.6 E-03 mrem
Dose to thyroid from bladder = 130 prem
Total dose to thyroid from all source organs from 50 μCi ^{125}I = 3.08 rem

Example 3

In a dual-tracer study involving apoA-I and apoA-II in which 25 μCi ^{131}I and 50 μCi ^{125}I label are administered, the total dose to thyroid is then the sum of the doses arising from each isotope. From examples 1 and 2, the total dose to the thyroid, which was blocked for only 1 day, is 1.21 + 3.08 = 4.29 rem.

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