NUKLEONIKA 2012;57(4):607–613

ORIGINAL PAPER

Biokinetics and radiation dosimetry for [4-^{14}C] cholesterol in humans

Larissa A. Marcato, Margarida M. Hamada, Carlos H. de Mesquita

Abstract. This study proposes a biokinetic model for using in the assessment of the internal dose received by human subjects administered intravenously or orally with [4-^{14}C]-cholesterol. The proposed model includes three systemic pools representing the short-term ($T_{1/2}$ = 1 d), intermediate-term ($T_{1/2}$ = 16 d) and long-term ($T_{1/2}$ = 78 d) physiological exchanges and two excretion pathways: urine and feces. To validate the model, the predicted excretion and absorption of cholesterol was compared with that described in the literature. The radiometric doses were calculated in function of the phantom body mass (M) applying MIRD (medical internal radiation dose) protocol with ANACOMP software. The effective dose coefficients for oral administration were: 2.93×10^{-10} Sv·Bq^{-1} (73.3 kg); 3.84×10^{-10} Sv·Bq^{-1} (56.8 kg); 6.74×10^{-10} Sv·Bq^{-1} (33.2 kg) and 7.72×10^{-10} Sv·Bq^{-1} (19.8 kg). To determinate the dose for intermediate body mass M the polynomial interpolation can be used: Sv·Bq^{-1} (kg) = 6×10^{-15}M^3 – 8×10^{-13}M^2 + 2×10^{-11}M + 6×10^{-10} ($R^2 \cong 1$). In the same way, for intravenous administration were: 3.72×10^{-10} Sv·Bq^{-1} (73.3 kg); 4.87×10^{-10} Sv·Bq^{-1} (56.8 kg); 8.49×10^{-10} Sv·Bq^{-1} (33.2 kg); 1.26×10^{-9} Sv·Bq^{-1} (19.8 kg). Similarly, for any M body mass: Sv·Bq^{-1} (kg) = -4×10^{-15}M^3 + 9×10^{-13}M^2 – 7×10^{-11}M + 2×10^{-9} can be used.

Key words: [4-^{14}C]-cholesterol • internal dosimetry • dosimetric model • medical internal radiation dose (MIRD)

L. A. Marcato, M. M. Hamada, C. H de Mesquita✉
Brazilian National Nuclear Energy Commission (CNEN/SP),
Institute for Nuclear and Energy Research (IPEN),
Radiation Technology Center (CTR),
2242 Prof. Lineu Prestes Ave., – Cidade Universitária,
05508-000, São Paulo – SP, Brazil,
Tel.: +55 11 3133 9829, Fax: +55 11 3133 9765,
E-mail: chmesqui@usp.br

Received: 26 October 2011
Accepted: 20 January 2012

Introduction

[4-^{14}C]-cholesterol is one of the most widely used radiotracers for biomedical research due to the importance of this compound in life maintenance and to understand the etiology of coronary heart diseases. Radiotracers constitute a simple and accurate tool for metabolic studies. However, the scientific community has shown objections concerning the use of radioisotopes in human subjects [2]. The risk of radioisotope incorporation can be evaluated by the dose parameter [18]. Physically, the absorbed dose D_T is defined as the ratio of radiation energy imparted in the body organ or tissue divided by its mass (kg). The absorbed dose depends on the time in which the radioactive material remains in the tissue and therefore the D_T is a subject to the radioisotope biodistribution in the body tissues along the time (biokinetic) [9]. Hence, the accuracy of the dose is very dependent on the kinetic model assumptions. The SI unit for absorbed dose is joule per kilogram and its special name is gray (Gy). It is known that the deleterious effects of radiation are dependent on several biological factors, such as the gender, age, previous health status, level of cells oxygenation, intake rate of the radiation (acute or chronic process) [13]. Furthermore, the effect of the dose to health also is greatly influenced by the type of radiation, for example, alpha-emitting radioisotopes are much more harmful

compared to the emitting beta and gamma radiation. Ideally, the dose should express the damage to health caused by the radiation exposure [13]. To achieve this idealized concept the scientific community defined a new dose notion called the equivalent dose, defined as: $H = w \times D$, where D is the already known absorbed dose and w is the weighting factor. Since w is dimensionless, the units are the same as for absorbed dose, J/kg, and its SI special name is sievert (Sv). The w ($= w_R \times w_N$) is a factor which is a combination of the radiation quality w_R (physical characteristic) and the biological effects w_N. The physical factor w_R is well defined in the literature and is associated with the LET (linear energy transfer) of the radiation. For α particles, fission fragments, and heavy ions w_R is assumed as equal to 20, for photons, electrons and muons (independently of their energies) w_R is assumed as equal to one and for neutrons w_R is assumed in the range of 5 to 20, depending on its energy [9, 10]. Unfortunately, in the current state of knowledge, the biological factors w_N were not tabulated. In the absence of its value, in practice, has been used $w_N = 1$, until better knowledge comes to light. A third definition of dose is necessary when only one or a specific set of organs are affected by the radiation. The deleterious impact of the absorbed dose to the health of these organs in the context of the whole body is defined by the weighted effective dose:

$$E = \sum w_T \cdot \left(\sum [(w_R - w_N) \cdot D_T \right)$$

where D_T is the average absorbed dose in the specific organ or tissue T. All three dose definitions: absorbed dose D, equivalent dose H and effective dose E have the same physical units (J/kg). Commonly, the absorbed dose D (gray) is used for inanimate objects and referring to a specific body tissue. The dose equivalent H (sievert) is used when referring to the whole body dose and the effective dose E (sievert) is applicable when only specific tissues are affected by the radiation.

In 1968, the Society of Nuclear Medicine developed a methodology for the calculation of internal dose known as MIRD Committee (medical internal radiation dose). The MIRD techniques describe a mathematical representation of the human body, which provide the absorbed fractions and radionuclide masses in organs. The MIRD formalism assumes that there are one or more organs that can concentrate radioisotopes (source organs). Their radiation can achieve itself and other organs (the target organs) [17].

The International Commission on Radiological Protection (ICRP) provides specific biokinetic models for a limited number of ^{14}C-labelled compounds only. For those compounds that do not have a described model, the generic radiocarbon model (GCM) is commonly used, as described in ICRP publications [9, 11]. The ICRP does not provide a specific biokinetic model for [4-^{14}C]-cholesterol, and in a such case, the GCM have been used. The GCM is based upon the average rate of carbon intake for Reference man [8] and it is assumed that ^{14}C-labelled compound is instantaneously and uniformly distributed in the body tissues and excreted with a half-life of 40 days [9, 11]. This model is useful for the element of ^{14}C which is very different for the case of the [4-^{14}C]-cholesterol molecule.

Taylor [19] calculated the effective dose coefficients for 27 ^{14}C-labelled molecular compounds (including [4-^{14}C]-cholesterol). The kinetic model proposed by Taylor is very similar to the GCM structure and uses kinetic data from the literature. The [4-^{14}C]-cholesterol model proposed by Taylor is based on kinetic data from Ref. [7]. Unfortunately, the Taylor's [18] model for the [4-^{14}C]-cholesterol uptake is exclusively intravenous. This can be considered a significant limitation, considering that the common uptake of cholesterol is by ingestion. Moreover, (a) the excretion profile from Taylor's model was not validated in terms of excretion (feces and urine) comparing to the model prediction with experimental data and (b) the model description is highly simplified and is unable to predict an overall view of the dose in different organs as can be previewed by the MIRD protocol. Taylor's model predicts an effective dose coefficient for injection of 3×10^{-10} Sv·Bq^{-1}. Assuming that Taylor's model is more realistic than GCM, despite its limitations described above, the GCM (5.8×10^{-10} Sv·Bq^{-1}) overestimates the dose in 93.3% in this case [9, 11]. The [4-^{14}C]-cholesterol internal dosimetry, taking into account the uptake by ingestion, still remains open in the literature.

Manger [14] proposed a generic model for systemic radiocarbon that is less conservative than the GCM [11] but maintains sufficient conservatism to avoid under--estimating the effective dose by most radiocarbon--compound-specific models. The Manger model is based upon common characteristics of current biokinetic models and excretion data derived from biokinetic studies in human subjects and rats. This model accounts for the short, moderate and long half-times that are present in many radiocarbon compounds that have been studied. Upon ingestion the radiocarbon proceeds according to the human alimentary tract model (HATM) described in ICRP Publication 30 [9]. The radiocarbon reaches the small intestine (SI) and it is rapidly absorbed and distributed to tissues by body fluids. In the Manger model, the excretion profile is based on the average of fourteen ^{14}C-labelled compounds. The profile of 60% in urine, 25% in breath and 15% in feces is used as a benchmark for the fine-tuning of the transfers coefficients. Meanwhile, the excretion profile of [4-^{14}C]--cholesterol is very different from these values. In the case of cholesterol, only 0.35 to 1.76% appeared in the urine, 99% is excreted on feces, no radioactivity is found in breath [7]. The percentage of cholesterol intestinal absorption varies from 15 to 75% in humans [6] against the 100% assumed by Manger's generic model. Therefore, a deep modification in the Manger's dosimetric model is required to fit the cholesterol biokinetic parameters.

The purpose of the present study was to define a new dosimetric model for [4-^{14}C]-cholesterol capable of assessing radiometric doses for oral and intravenous [4-^{14}C]-cholesterol uptake. To validate the proposed model, the excretion and absorption profiles of [4-^{14}C]--cholesterol, for human subjects, were compared with those described in the literature [1–3]. The radiometric doses were calculated by means the MIRD protocol [15] using the ANACOMP software [15] for theoretical phantoms described in ICRP publication "Reference man" [8].

Model fundamentals

[4-^{14}C]-cholesterol excretion data

Hellman *et al*. [7] reported that no radioactivity was found in expired air after the [4-^{14}C]-cholesterol administration; indicating that as little as 0.1 per cent of the administered dose per day could have been detected by the method used. The fact that no labelled carbon dioxide was detected after the administration of [4-^{14}C]--cholesterol shows that ^{14}C remained attached to the rest of the cholesterol nucleus [7]. Others references [12] exclude the possibility of [4-^{14}C]-cholesterol excretion in $^{14}CO_2$ form.

Experimental results for [4-^{14}C]-cholesterol in humans show that the plasma peak specific activity is not reached until approximately the second or third day after ingestion [1–3, 6, 7, 16]. The percentage of cholesterol intestinal absorption investigated with radioactive tracers varies from 15 to 75% in humans [6], a broad range suggestive of metabolic or genetic regulation [2]. The efficiency of absorption also may be related to the large difference in the amount of food intake, Borgstrom [1] reported the averages of 45.7 ± 6.1% for 150 mg, 48.5 ± 15.0% for 550 mg), 33.3 ± 10.0% for 950 mg and 22.8 ± 2.6% for 1910 mg. All cited values for cholesterol absorption are from normal subjects.

In the present study, data from 43 normal subjects both sexes in the range of 16 to 49 year old described in Refs. [1, 3] were used to estimate the cholesterol absorption trend in function of the amount of ingested cholesterol. The amount of percent cholesterol absorbed was linearly related to dose fed over the range from 110 to 1910 mg (Fig. 1). The predicted equation for calculating the cholesterol absorption is shown in Eq. (1):

$$C_{\text{absorbed}} = 50 - 0.014 \cdot C_{\text{ingested}} \quad (1)$$

where C_{absorbed} is the amount of cholesterol absorbed (%) and C_{ingested} (mg) is the amount of cholesterol ingested in a single test meal.

In published studies [1, 3] the radioactivity of the non-absorbed dietary cholesterol was determined in daily fecal samples over six days to provide an estimate of the absorbed cholesterol. Most of the non-absorbed cholesterol appeared in fecal samples on the second or third day after meal ingestion and the total of the non--absorbed cholesterol was recovered over 6 days [1, 3].

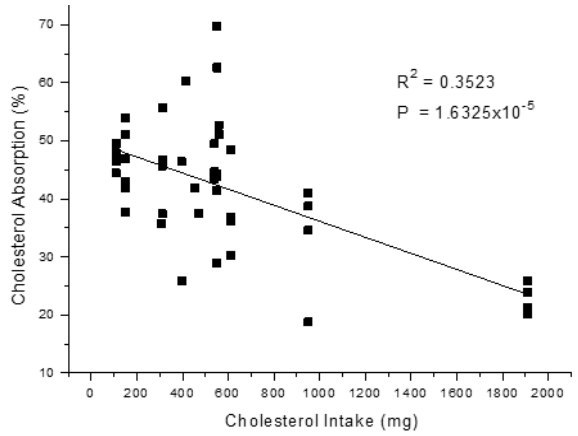

Fig. 1. The cholesterol absorption (%) of 43 normal subjects after the ingestion of a single test meal containing different amounts of cholesterol (mg). The data are derived from Refs. [1, 3].

Table 1. Cumulative [4-^{14}C]-cholesterol radioactivity recovered in feces in function of time after cholesterol uptake (days). The data are from 43 normal subjects that ingested a single test meal containing different amounts of cholesterol (110 to 1950 mg), the data are derived from Refs. [1, 3]

Time (days)	Cumulative radioactivities (%)
1	7.22 ± 10.15
2	34.21 ± 21.30
3	47.44 ± 20.15
4	53.65 ± 16.69
5	57.19 ± 12.50
6	58.01 ± 12.90

In this study, data from 43 normal subjects derived from Refs. [1, 3] were used to calculate the average cholesterol excretion in function of time after ingestion. The amount of [4-^{14}C]-cholesterol ingested by the subjects of the select data varied from 110 to 1910 mg. The cholesterol excretion average for the range of six days is listed in Table 1.

Only 0.35 to 1.76% of the ingested [4-^{14}C]-cholesterol appeared in the urine since the kidney is a minor route for the excretion of the cholesterol nucleus. Considerable fractions of radioactivity in the urine are from metabolites of steroid hormones [7].

Biokinetic model

The [4-^{14}C]-cholesterol model proposed was based in experimental data described in the literature, ICRP Publication 30 [1, 3, 7, 9]. It is important to observe that the proposed model is limited to tracers capable of following the cholesterol molecule through its entire metabolic pathway, as is in the case of [4-^{14}C]--cholesterol. Some tracers like the ^{14}C-cholesteryl oleate, which is labelled in the fatty acid portion of molecule, can be hydrolyzed and deviate from the cholesterol pathway core.

The structure of the kinetic model contains nine compartments (Fig. 2). The pathway of [4-^{14}C]-cholesterol uptake is through ingestion and the input of the labelled particle is represented by an arrow with asterisk (C_1 or C_5). The pathways of excretion considered are renal (C_9) and fecal (C_4). No measurable ^{14}C activity was reported in expired air after [4-^{14}C]-cholesterol administration [7, 12] thus this excretion pathway was not included in the model. Furthermore, comparing the proposed model with the Manger model [7] it was included one more systemic pool of cholesterol exchange (moderate-term, $T_{1/2}$ = 16 d) and the colon is divided in two compartments (ULI and LLI) in agreement with ICRP 30 [9] and Eve model [4, 5].

Upon ingestion the [4-^{14}C]-cholesterol proceeds according to the HATM described in ICRP 30 [9]. The ingested [4-^{14}C]-cholesterol reaches the small intestine (C_2) and is absorbed into the bloodstream (C_5). The [4-^{14}C]-cholesterol that reaches the blood is transferred to urinary bladder and to three systemic pools representing the short-term ($T_{1/2}$ = 1 d), moderate-term

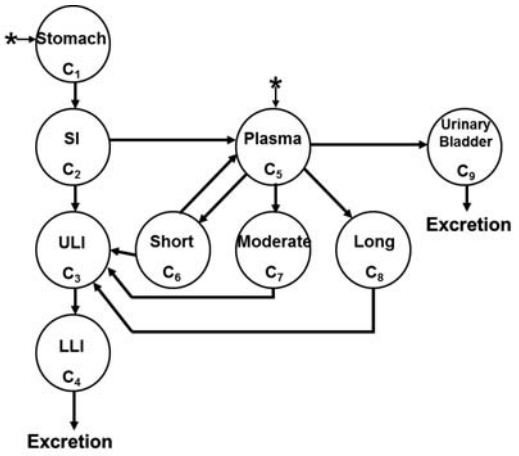

Fig. 2. Proposed biokinetic model for [4-^{14}C]-cholesterol. C_1 – stomach; C_2 – small intestine (SI); C_3 – upper large intestine (ULI); C_4 – lower large intestine (LLI); C_5 – blood; C_6 – systemic short ($T_{1/2}$ = 1 d); C_7 – systemic moderate ($T_{1/2}$ = 16 d); C_8 – systemic long ($T_{1/2}$ = 78 d) and C_9 – urinary bladder. The input of the [4-^{14}C]-cholesterol is represented by an asterisk.

($T_{1/2}$ = 16 d) and long-term ($T_{1/2}$ = 78 d) physiological exchanges of cholesterol between the body tissues [7, 19]. The $k_{i,j}$ parameters (Table 2) represent the transfer fractions of material from compartment i (C_i) to compartment j (C_j) and are associated with the biological half-life by the equation $k_{i,j} = \log_e(2) / T_{1/2}$. Constants $k_{1,2}$, $k_{3,4}$, and $k_{4,0}$ are derived from Ref. [9]. $k_{6,3}$, $k_{7,3}$ and $k_{8,3}$ are derived from [7] and $k_{9,0}$ from Ref. [19]. The parameters $k_{2,3}$ (SI to ULI) and $k_{2,5}$ (SI to blood) can be calculated in function of the amount of cholesterol ingestion by Eqs. (2) and (3) respectively:

$$k_{2,3} = \left[1 - \left(\frac{50 - 0.014 \cdot C_{\text{ingested}}}{100}\right)\right] \cdot 0.115 \quad (2)$$

$$k_{2,5} = \frac{(50 - 0.014 \cdot C_{\text{ingested}})}{100} \cdot 0.115 \quad (3)$$

Further $k_{i,j}$ were estimated by fitting procedure using the model shown in Fig. 2 applied to data from Fig. 3.

Table 2. Transfer coefficients for the proposed [4-^{14}C]--cholesterol biokinetic model

Pathway	Transfer coefficient (d^{-1})
$k_{1,2}$ (stomach to SI)	24 [9]
$k_{2,3}$ (SI to ULI)	Eq. (2)
$k_{2,5}$ (SI to blood)	Eq. (3)
$k_{3,4}$ (ULI to LLI)	1.8 [9]
$k_{4,0}$ (LLI to excreta)	1 [9]
$k_{5,6}$ (blood to short)	1.5*
$k_{5,7}$ (blood to moderate)	0.03*
$k_{5,8}$ (blood to long)	0.002*
$k_{5,9}$ (blood to bladder)	0.002*
$k_{9,0}$ (bladder to excreta)	0.693 [19]
$k_{6,5}$ (short to blood)	13.44*
$k_{6,3}$ (short to ULI)	0.693 [7]
$k_{7,3}$ (moderate to ULI)	0.0433 [7]
$k_{8,3}$ (long to ULI)	0.009 [7]

Parameters labelled with (*) were estimated by fitting using data.

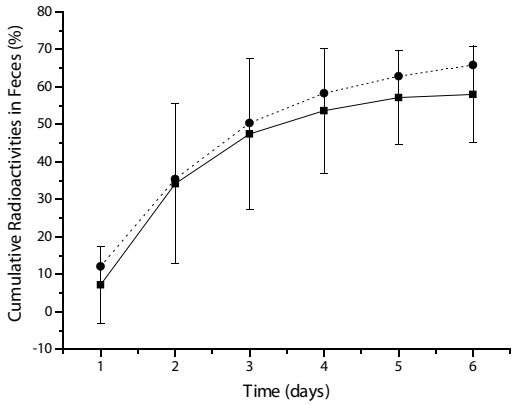

Fig. 3. Average of the cumulative fecal radioactivity in function of time after [4-^{1}4C]-cholesterol ingestion. (■) Experimental data from 43 normal subjects derived from [1] and [3]. The bars represent the standard deviation. (●) Predicted by the proposed kinetic model.

Statistical analysis

The statistical analysis was performed with the software SigmaStat Version 1.0 (Systat Software Inc., USA).

Results and discussion

Validation of the proposed model

Excretion profile after [4-^{14}C]-cholesterol ingestion

In order to validate the proposed model, the predicted values were compared with the experimental data (Fig. 3) [1, 3]. The [4-^{14}C]-cholesterol excretion profile predicted by the proposed model was compared with the excretion profile listed in Table 1. The ingestion for the same amounts of cholesterol (110 to 1910 mg) was simulated for the proposed model and the weighted average calculated. There was no statistically significant difference between the excretion profiles according to the Kruskal-Wallis test (P = 0.416).

Double tracer ratio profile after [4-^{14}C]-cholesterol uptake

Zilversmit [21] proposed a method to determine cholesterol absorption that involved only the analysis of plasma radioactivity. It required the simultaneous administration of two tracers of cholesterol, for example: ^{14}C- and ^{3}H-labelled cholesterol [16]. One of them is given orally and the other intravenously, and subsequent comparison of two plasma cholesterol specific activity curves was carried out [16]. The percent absorption can be calculated as the ratio of the two radioactivities in the plasma (for example, intake of ^{3}H-tracer orally to ^{14}C-tracer intravenously) after the ratio normalization [2, 16, 21]. A critical requirement of the isotope ratio method is that the body metabolizes the two radioisotopic cholesterols identically [16].

In this report, the Zilversmit method was performed by the proposed model. An input was carried out in the compartment C_5 (plasma) to simulate the intravenous

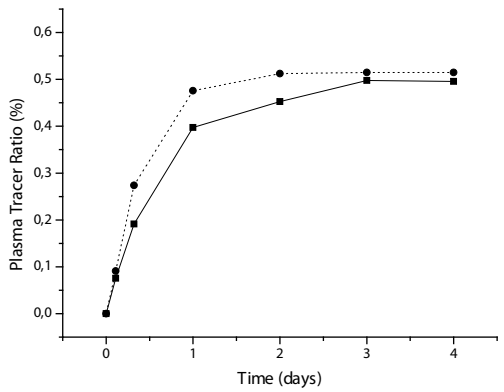

Fig. 4. Plasma tracer ratio in function of time after [4-^{14}C]--cholesterol uptake. (●) Predicted by the proposed kinetic model. (■) Experimental data from Bosner *et al*. [2].

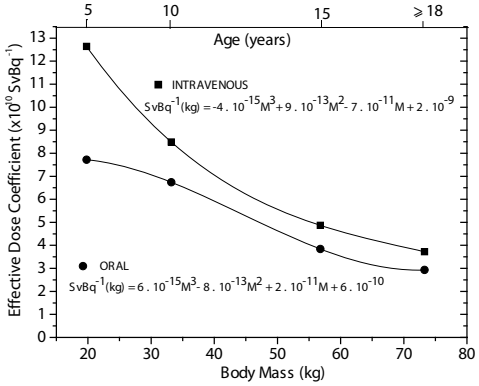

Fig. 5. Effective dose coefficients in function of phantoms body mass for: (■) intravenous [4-^{14}C]-cholesterol intake and (●) oral [4-^{14}C]-cholesterol intake (400 mg).

intake. Whereas 30 mg of cholesterol was inserted in the compartment C_1 (stomach) to represents the oral administration. Subsequently, the plasma tracer ratio curve was plotted.

The plasma tracer ratio curve predicted by the proposed model was compared with that reported by Bosner *et al*. [2] for a single normal subject who ingested a single test meal containing 30 mg of cholesterol (Fig. 4). There was no statistically significant difference between them according to the Kruskal-Wallis test (P = 0.423).

The cholesterol absorption depends on a number of factors as dietary habits, age, physical activity, genetics and others. In Fig. 1 the ingestion is responsible only for ~35% (R^2 = 0.3523) of the scattering data. The remaining is due to others causes of variation. Therefore, the absorption as a function of intake should be used with cautiousness since it serves only as a trend value. Ethical committees are formed by experts and should use the parameter absorption according to their knowledge and use the parameters $k_{2,3}$ and $k_{2,5}$, according to their specificities.

Calculation of the radiation dose

The radiometric doses were determined using the MIRD protocol [17] by means of the ANACOMP software computer [15], which calculates the radiometric doses using the kinetic parameters $k_{i,j}$ (listed in Table 2) from the compartmental model shown in Fig. 3. The effective doses and the absorbed dose in organs were calculated according to ICRP Publications 60 [10] in function of the phantoms body mass. The theoretical phantoms can represent an adult (73.7 kg), a 15 years old adolescent (56.8 kg), a 10 years old child (33.2 kg) and a 5 years old child (19.8 kg).

Internal dosimetry for [4-^{14}C]-cholesterol – oral intake

The radiometric doses were calculated by an uptake of 400 mg of cholesterol, the input of the radiolabelled cholesterol is represented by the arrow with asterisk in the compartment C_1 (stomach). The effective dose coefficients (Sv·Bq^{-1}) are shown in Fig. 5 and the absorbed dose coefficients to various organs and tissues are listed in Table 3.

Internal dosimetry for [4-^{14}C]-cholesterol – intravenous intake

The input of the radiolabelled cholesterol is represented by the arrow with asterisk in the compartment C_5 (plasma). The effective dose coefficients (Sv·Bq^{-1}) are shown in Fig. 5 and the absorbed dose coefficient to various organs and tissues are listed in Table 3.

For the same administered activity, the effective dose coefficient decreases with the body mass increase. In other words, for the same intake activity, individuals with low body mass are submitted to higher doses. In this study a third order polynomial was used to interpolate the dose effective coefficient for unknown body mass (Fig. 5). The polynomial model showed a high quality of agreement ($R^2 \cong 1$).

The ICRP 60 [10] recommends that any activities that require radioactive sources should not expose public person to an effective dose greater than 1 mSv/y. Adopting this dose level as acceptable to submit volunteers to metabolic studies with [4-^{14}C]-cholesterol, the amount of radioactive tracer for a single dose that can be administered orally could be: ≤3.4 MBq (91.9 μCi) for adults, ≤2.61 MBq (70.5 μCi) for 15 years old adolescent, ≤1.48 MBq (40.0 μCi) for 10 years old child and 1.30 MBq (35.1 μCi) for 5 years old child. Similarly, using the same 1 mSv/year as the reasonable safety limit then the amount of radioactive tracer that can be administered intravenously could be: ≤ 2.69 MBq (64.6 μCi) for adults, ≤ 2.05 MBq (55.4 μCi) for 15 years old adolescent, ≤ 1.18 MBq (31.9 μCi) for 10 years old child and ≤ 0.79 MBq (21.4 μCi) for 5 years old child. Intravenous intake is more restrictive than oral because in the second case the oral intake involves only ~50% tracer absorption. The non-absorbed fraction is excreted in feces in few days (Fig. 3), while the absorbed fraction (~50%) will be retain for several days according to the moderate-term ($T_{1/2}$ = 16 d) and long-term ($T_{1/2}$ = 78 d) pools of physiological exchanges of cholesterol between the body tissues.

Most studies that utilize [4-^{14}C]-cholesterol commonly use radioactivity in the range 3.7 to 185 kBq (1 to 50 μCi) [1, 3, 6, 7, 21]. In such cases, the effective dose will be 0.0011 to 0.233 mSv which is lower than the 1 mSv allowed as acceptable dose for a person/year.

Table 3. Absorbed dose coefficients for oral and intravenous [4-^{14}C]-cholesterol intake

Organs	Absorbed dose coefficient (Gy·Bq^{-1})							
	Adult (73.73 kg)		15 years old (56.8 kg)		10 years old (33.2 kg)		5 years old (19.8 kg)	
	Oral	Intravenous	Oral	Intravenous	Oral	Intravenous	Oral	Intravenous
Adrenals	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Brain	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Breast	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Gallbladder	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
LLI	2.45×10^{-9}	2.52×10^{-9}	3.21×10^{-9}	3.32×10^{-9}	5.67×10^{-9}	5.83×10^{-9}	7.43×10^{-9}	7.83×10^{-9}
SI	3.69×10^{-10}	1.76×10^{-10}	4.84×10^{-10}	2.29×10^{-10}	8.62×10^{-10}	3.91×10^{-10}	7.28×10^{-10}	6.56×10^{-10}
Stomach	1.33×10^{-10}	1.76×10^{-10}	1.75×10^{-10}	2.29×10^{-10}	2.81×10^{-10}	3.91×10^{-10}	3.36×10^{-10}	6.56×10^{-10}
ULI	8.89×10^{-10}	9.80×10^{-10}	1.17×10^{-9}	1.29×10^{-9}	2.10×10^{-9}	2.30×10^{-9}	2.64×10^{-9}	3.12×10^{-9}
Heart	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Kidneys	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Liver	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Lungs	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Muscle	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Ovaries	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Pancreas	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Bone marrow	9.65×10^{-11}	2.17×10^{-10}	1.27×10^{-10}	2.87×10^{-10}	2.20×10^{-10}	4.95×10^{-10}	1.89×10^{-10}	8.50×10^{-10}
Cortical bone	7.50×10^{-11}	1.69×10^{-10}	9.52×10^{-11}	2.14×10^{-10}	1.60×10^{-10}	3.60×10^{-10}	1.30×10^{-10}	5.85×10^{-10}
Skin	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Spleen	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Testicles	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Thymus	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Thyroid	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Urinary bladder	9.79×10^{-11}	2.20×10^{-10}	1.27×10^{-10}	2.29×10^{-10}	2.14×10^{-10}	4.81×10^{-10}	1.78×10^{-10}	7.80×10^{-10}
Womb	7.83×10^{-11}	1.76×10^{-10}	1.02×10^{-10}	2.29×10^{-10}	1.74×10^{-10}	3.91×10^{-10}	1.46×10^{-10}	6.56×10^{-10}
Effective dose (Sv·Bq^{-1})	2.93×10^{-10}	3.72×10^{-10}	3.83×10^{-10}	4.87×10^{-10}	6.74×10^{-10}	8.49×10^{-10}	7.72×10^{-10}	1.26×10^{-9}

In other words, these dose levels are lower than the environmental dose from the sum of cosmic rays (gamma rays and X-rays from space) and radiation from ^{238}U, ^{236}Th, ^{40}K, ^{14}C found naturally in the earth. About half of the total annual average U.S. individual's radiation exposure comes from natural sources. Another half is mostly from diagnostic medical procedures. For the American population, the average annual radiation exposure from natural sources is about 3.1 mSv/y. Radon and thoron gases account for two-thirds of this exposure, while cosmic, terrestrial, and internal radiation account for the remainder. No adverse health effects have been related from doses arising from these levels of natural radiation exposure [20].

Conclusions

The proposed kinetic model achieves an adequate level of agreement between the calculated cholesterol excretion and experimental values reported in published studies [1, 3]. The model was capable of reproducing the Zilvermit double tracer ratio method and no statistically significant difference between predicted values and the experimental data from the literature [2] was observed. For the same administered activity, the effective dose coefficient decreases with the body mass increase. The effective dose coefficients vs. body mass can be expressed by a third order polynomial. Most studies that utilize [4-^{14}C]-cholesterol commonly use radioactivity in the range 37 to 185 kBq (1 to 50 μCi) for adults [1, 3, 6, 7, 21]. Adopting 1 mSv/year as acceptable to submit volunteers to metabolic studies, in such cases, the effective dose coefficients will be in the range 0.012 to 0.54 mSv for an adult for oral administration, which is lower than the 1 mSv allowed as acceptable dose for public subject/year.

Acknowledgment. The authors wish to thank CAPES for financial support.

References

1. Borgstrom B (1969) Quantification of cholesterol absorption in man by fecal analysis after the feeding of a single isotope-labeled meal. J Lipid Res 10:331–337
2. Bosner MS, Ostlung RE, Osofisan O, Grosklos J, Fritschle C, Lange LG (1993) Assesment of percent cholesterol absorption in humans with stable isotopes. J Lipid Res 34:1047–1053
3. Connor WE, Lin DS (1974) The intestinal absorption of dietary cholesterol by hypercholesterolemic (type II) and normocholesterolemic humans. J Clin Invest 53:1062–1070
4. Dolphin GW, Eve IS (1966) Dosimetry of gastrointestinal tract. Health Phys 12:163–172
5. Eve IS (1966) A review of the physiology of the gastrointestinal tract in relation to radiation doses from radioactive materials. Health Phys 12:131–161
6. Grundy SM, Mok HYI (1977) Determination of cholesterol absorption in man by intestinal perfusion. J Lipid Res 18:263–271
7. Hellman L, Rosenfeld RS, Eidinoff ML *et al*. (1955) Isotopic studies of plasma cholesterol of endogenous and exogenous origin. J Clin Invest 34:48–60
8. ICRP (1975) Reference man: anatomical, physiological and metabolic characteristics. ICRP Publication 23. International Commission on Radiological Protection
9. ICRP (1979) Limits for intakes of radionuclides by workers. ICRP Publication 30. International Commission on Radiological Protection
10. ICRP (1991) Recommendations radiological protection. ICRP Publication 60. International Commission on Radiological Protection
11. ICRP (1995) Age-dependent doses to members of the public from intake of radionuclides. ICRP Publication 71. International Commission on Radiological Protection
12. Levitt MD, Hanson RF, Bond JH, Engel RR (1975) Failure to demonstrate degradation of [4-^{14}C] cholesterol to volatile hydrocarbons in rats and in human fecal homogenates. Lipids 10:662–666
13. Makrigioros GM, Ito S, Baranowska-Kortiylewicz J (1990) Inhomogeneous deposition of radiopharmaceuticals at a cellular level: experimental evidence and dosimetric implications. J Nucl Med 31:1358–1363
14. Manger RP (2011) A generic biokinetic model for carbon-14. Radiat Prot Dosim 143:42–51
15. Marchese SR, Mesquita CH, Cunha IIL (1998) AnaComp program application to calculate ^{137}Cs transfer rates in marine organisms and dose on the man. J Radioanal Nucl Chem 232:233–236
16. Samuel P, Crouse JR, Ahrens EHJ (1978) Evaluation of an isotope ratio method for measurement of cholesterol absorption in man. J Lipid Res 19:82–93
17. Stabin MG, Tagesson M, Thomas SR, Ljungberg M, Strand SE (1999) Radiation dosimetry in nuclear medicine. Appl Radiat Isot 50:73–87
18. Taylor DM (2000) Generic models for radionuclide dosimetry ^{11}C-, ^{18}F- or ^{75}Se-labelled amino acids. Appl Radiat Isot 52:911–922
19. Taylor DM (2004) Biokinetic model for the behavior of carbon-14 from labeled compounds in the human body: can a single model be justified? Radiat Prot Dosim 108:187–202
20. USNRC (2010) Radiation protection and the NRC. NUREG/BR-0322. United States Nuclear Regulatory Commission, Washington
21. Zilversmit DB, Hughes LB (1974) Validation of a dual-isotope plasma ratio method for measurement of cholesterol absorption in rats. J Lipid Res 15:465–473