

**A GENERIC BIOKINETIC MODEL FOR C-14 LABELLED
COMPOUNDS**

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A GENERIC BIOKINETIC MODEL FOR C-14 LABELLED COMPOUNDS

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SUMMARY

Carbon-14, a radioactive nuclide, is used in many industrial applications. Due to its wide range of uses in industry, many workers are at risk of accidental internal exposure to ^{14}C . Being a low energy beta emitter, ^{14}C is not a significant external radiation hazard, but the internal consequences posed by ^{14}C are important, especially because of its long half life of 5730 years [46]. The current biokinetic model recommended by the International Commission on Radiological Protection (ICRP) is a conservative estimate of how radiocarbon is treated by the human body. The ICRP generic radiocarbon model consists of a single compartment representing the entire human body. This compartment has a biological half life of 40 days yielding an effective dose coefficient of $5.8 \times 10^{-10} \text{ Sv Bq}^{-1}$ [44, 45, 49, 53, 54]. This overestimates the dose of all radiocarbon compounds that have been studied [96].

An improved model has been developed that includes and alimentary tract, a urinary bladder, CO_2 model, and an “Other” compartment used to model systemic tissues. The model can be adapted to replicate any excretion curve and excretion pattern. In addition, the effective dose coefficient produced by the updated model is near the mean effective dose coefficient of carbon compounds that have been considered in this research. The major areas of improvement are: more anatomically significant, a less conservative dose coefficient, and the ability to manipulate the model for known excretion data. Due to the wide variety of carbon compounds, it is suggested that specific biokinetic models be implemented for known radiocarbon substances. If the source of radiocarbon is dietary, then the physiologically based model proposed by Whillans [102]

that splits all ingested radiocarbon compounds into carbohydrates, fats, and proteins should be used.

CHAPTER 1: INTRODUCTION

Carbon-14 is a long-lived radioactive nuclide with a half life of 5.73×10^3 years. It emits one beta particle per decay with an average energy of 49.5 keV [46]. Being a long-lived beta emitter, carbon-14 is not a significant external radiation hazard, yet it presents a considerable threat if it becomes internally deposited within the human body.

Carbon is present in many forms in nature and as a product of industry. Not only can carbon be found in gas, liquid, and solid state at standard temperature and pressure, but it is also present in various chemical forms within those states of matter. With such a large variation in its chemical properties and state, carbon-based compounds are treated in a non-uniform way by the human body. Some compounds may be totally excreted in the urine, while others may be totally excreted in the breath or feces. Regardless of the method of uptake (ingestion, inhalation, or injection/wound), the excreta pathway will vary from primarily fecal to primarily urine to primarily breath. This wide variation in excreta pathways signifies that radiocarbon compounds may have a large variation in its dose coefficients.

Much research has been performed in attempt to develop a generic model to be used to estimate dose following the uptake of an unknown carbon compound. The current widely-accepted model is the International Commission on Radiological Protection's (ICRP) recommendation from ICRP Publication 30 that suggests a 40 day total body half life for any radiocarbon substances [44,45]. This half life was determined by performing a mass balance on the human body, assuming the unit-rate of carbon turnover is

equivalent to the average daily carbon intake, 0.3 kg d^{-1} , of Reference Man [43] divided by the total mass of carbon in the body of reference man, 16kg. This 40 half life yields a dose coefficient of $5.8 \times 10^{-10} \text{ Sv Bq}^{-1}$ when using the ICRP 60 tissue weighting coefficients [50]. This dose coefficient overestimates the dose for most carbon compounds. For carbon monoxide, the dose is overestimated by a factor of 725 [45, 55]. This large overestimate of dose could result in an excessively conservative dose estimate. An updated generic model that represents a more “central” dose estimate should be considered, using scientific studies to generate the compartment model and the corresponding biological half-lives.

CHAPTER 2: BACKGROUND

A few attempts have been made to create a generic model for radiocarbon compounds. The initial generic radiocarbon model was created by the ICRP. In this model, the body is depicted as being a single well-mixed pool with a removal half-time of 40 days. This half time is based on a balance of the carbon intake and excretion of Reference Man (Equation 2. 1).

$$T_{1/2} = \ln 2 \times \frac{\text{Total mass of carbon in the body}}{\text{Average daily carbon intake}} \quad [\text{Equation 2.1}]$$

The total body mass of carbon for Reference Man is 16 kg and the average daily carbon intake is 0.3 kg d⁻¹ [43]. This yields a biological half life of 37 days, which has been rounded up to 40 days for radiological protection purposes. The structure of the generic model is displayed in Figure 2.1, where the unit biological transfer rate is presented as λ .

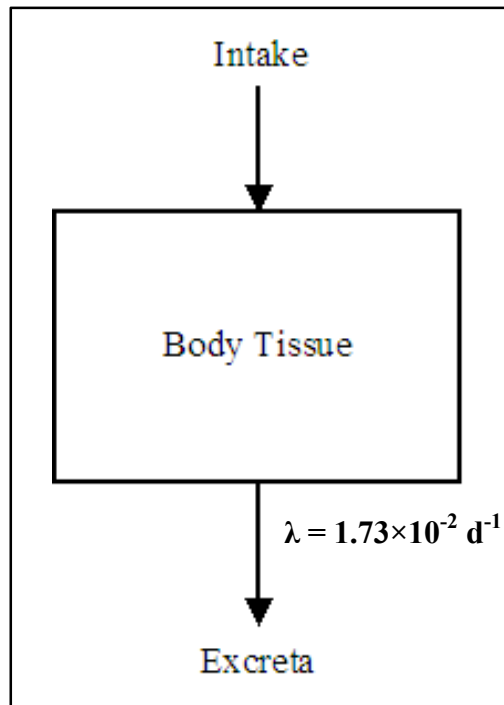


Figure 2.1 ICRP generic biokinetic model for radiocarbon labelled substances.

The generic ICRP radiocarbon biokinetic model is lacking in anatomical detail and tends to overestimate the dose. Much research has been performed in attempt to improve upon the current generic carbon model (GCM) recommended by the ICRP. A biochemical-based biokinetic model for the dosimetry of dietary organically bound tritium was developed by Richardson and Dunford [82, 83]. The form of the metabolic model enables the creation of a model for carbon-14. The advantage of a physiologically based model is that a broad range of anatomical and metabolic information can be incorporated. In addition, the models may be easily adjusted for people of different ages and genders. The model created by Richardson and Dunford, the HCNO model (able to model dietary H – hydrogen, C – carbon, N – nitrogen, and O – oxygen), was presented in a simplified version, HCNO-S, and a complex version, HCNO-C.

The HCNO models are based upon the overall metabolic reactions of carbohydrates, fats, and proteins, the building blocks of dietary substances. In the same manner as the ICRP GCM, the rate constants are determined via the quotient of the daily carbon intake by the carbon pool size. Having more compartments than the GCM, a carbon balance was determined for each of the compartments in the model, yet the model was presented for tritium, therefore the transfer rates are not available for the carbon version of the HCNO models. A visual representation of the HCNO-S model is displayed in Figure 2.2. The non-anatomical compartments in the model are carbohydrates, proteins, lipids, and fats. The remainder of the model is made up of ICRP models for the respiratory tract, gastrointestinal tract, urinary bladder, and bone compartments.

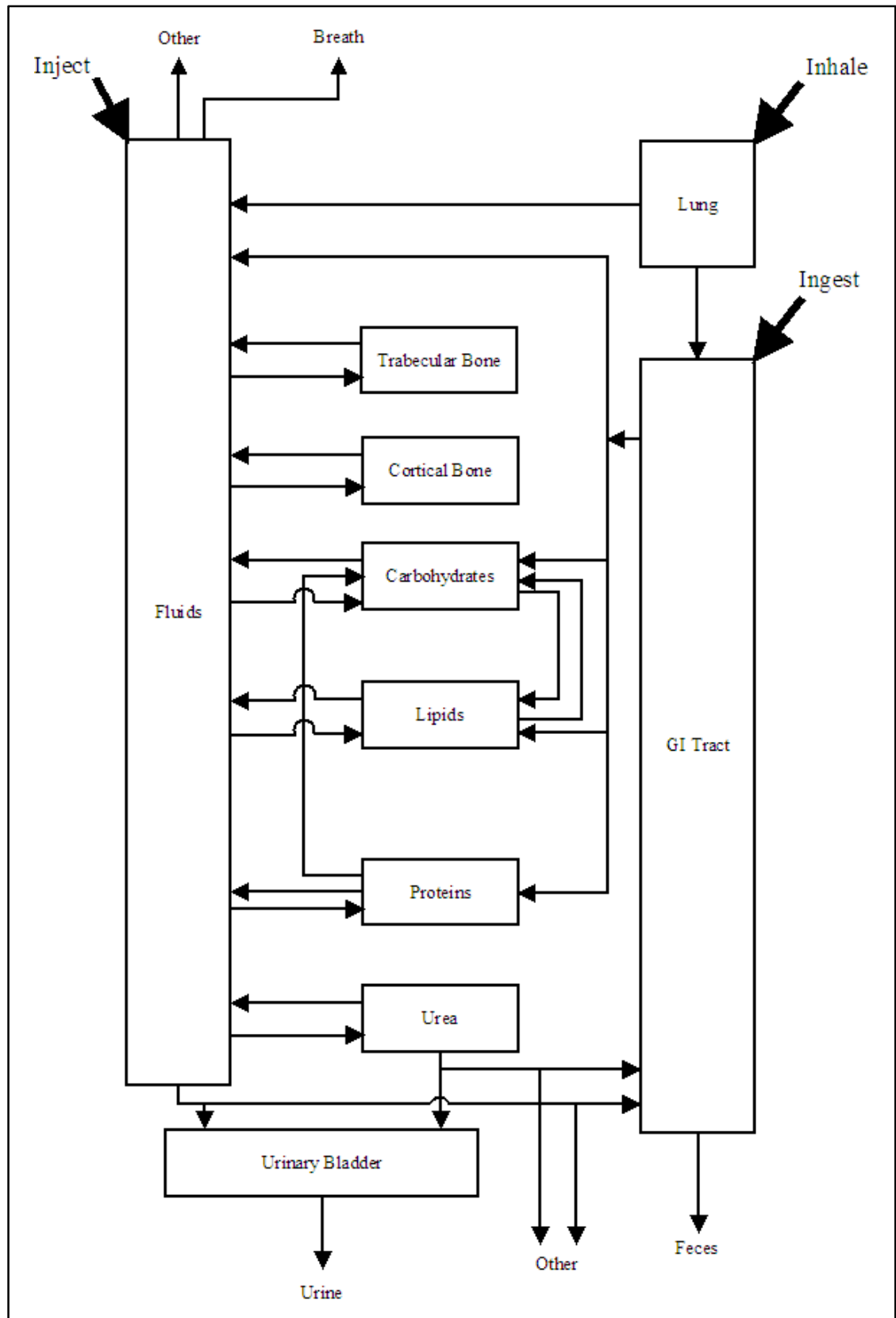


Figure 2.2 The HCNO-S Model proposed by Richardson and Dunford

Another model attempting to describe the biokinetics of radiocarbon was created by Whillans [102]. The model created by Whillans shares many features with the HCNO models, but it is intended for intakes of organic carbon-14 and $^{14}\text{CO}_2$ as opposed to strictly dietary carbon, as in the case of the HCNO model. The model proposed by Whillans is a physiologically based biokinetic (PBBK) model, which divides all dietary intakes into carbohydrates, fat, and protein while including a carbon dioxide/bicarbonate (CO_2/HCO_3) pool as the central transfer compartment. The transfer rates in the model are based upon the nominal intakes of Reference Man and transfer rates recommended by Brown and Chant [8]. The structure of the PBBK model is presented in Figure 2.3. In Figure 2.3, Trabecular bone is TB, bone surface is BS, cortical bone is CB, carbohydrates are CHO, and the carbon dioxide/bicarbonate pool is CO_2/HCO_3 .

The inclusion of a central bicarbonate compartment is based upon the premise that carbon dioxide is produced via cellular respiration, or metabolism. Regardless of the carbon compound entering the body, carbon dioxide may be produced as a product of metabolizing the compound. Bicarbonate ions, HCO_3^- are the main form (~80%) that CO_2 is transported through the blood. HCO_3^- is formed by the enzyme carbonic anhydrase in the red blood cells via the reaction $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$ [72]. The PBBK model proposed by Whillans improves upon the HCNO model due to the addition of a bicarbonate pool, yet it neglects to explicitly consider the ICRP gastrointestinal tract, respiratory tract, and urinary bladder models.

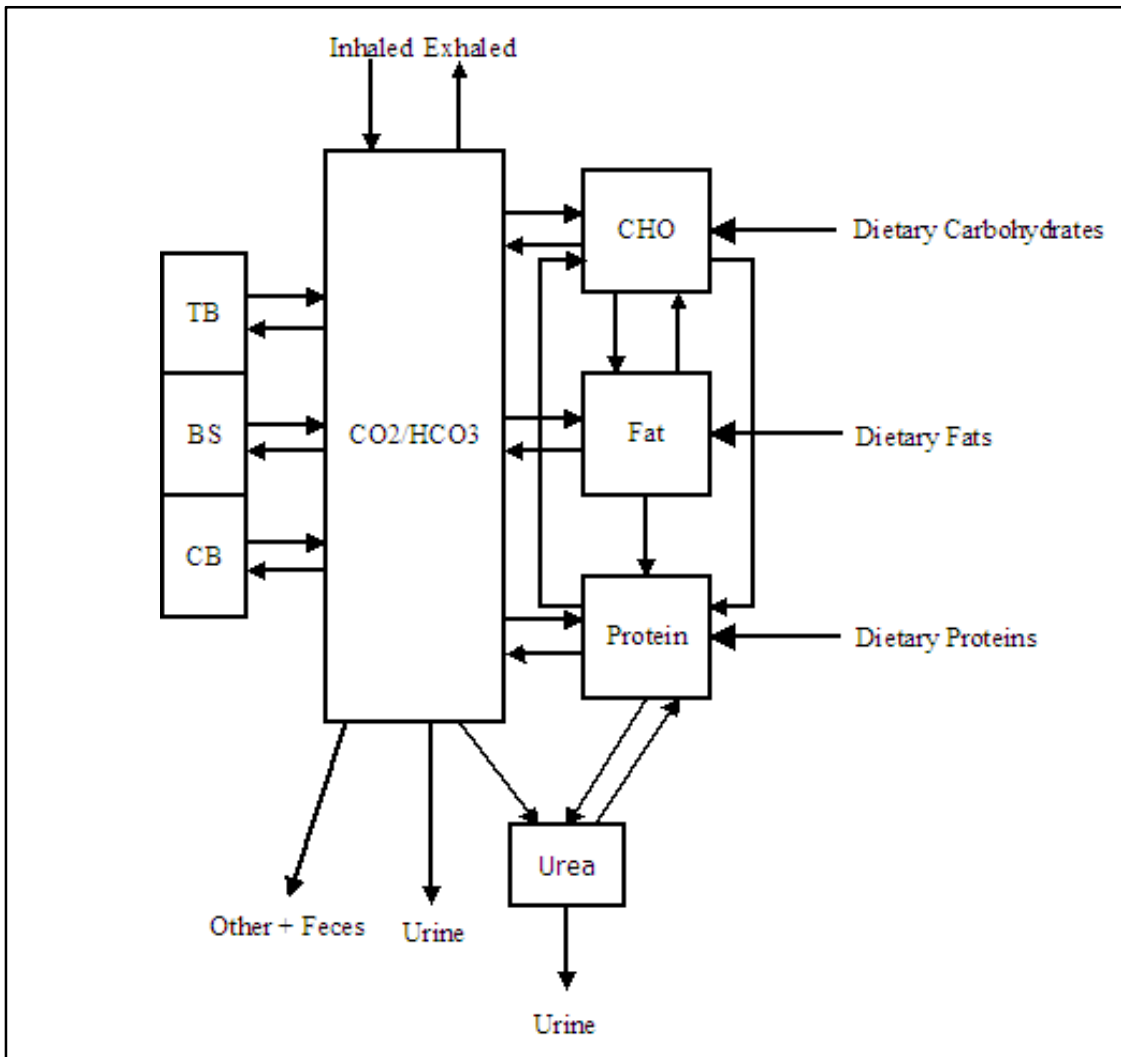


Figure 2.3 PBBK carbon model structure proposed by Whillans

In 2009, another generic model was proposed by Galeriu et al. to describe the dynamic transfer of carbon-14 and tritium in mammals [27, 28]. The transfer rates in this model are determined by using metabolic rates, assuming the energy expenditure of a mammal will dictate the rate at which an internally deposited compound will be excreted from the body. The model is not based upon experimental data for any specific radiocarbon or tritiated compounds because the assumption is made by the author that experimental data are sparse and a more generic approach would be more resource-effective. The primary difference between the model proposed by Galeriu et al. and the HCNO and PBBK models is that the transfer rates are based upon both Reference Man intake data and metabolic rates. The model is presented in Figure 2.4.

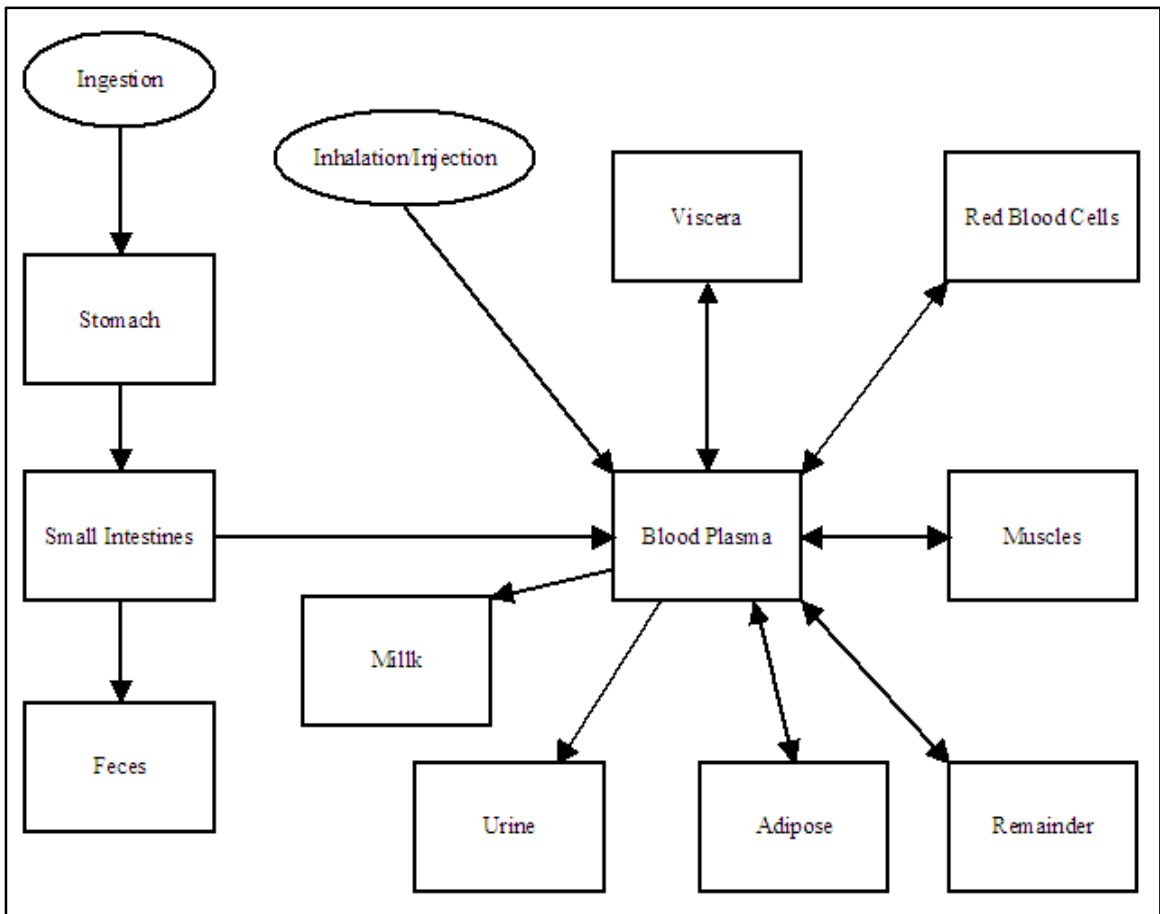


Figure 2.4 Generic radiocarbon model proposed by Galeriu

The models proposed by Galeriu et al., Richardson and Dunford, and Whillans are improvements upon the GCM, but their uses are restricted. The HCNO models may only be used for dietary radiocarbon, the PBBK model of Whillans may only be used for CO₂ and dietary carbon, and the model proposed by Galeriu may only be used for dietary intakes and some specific chemical forms. When considering more exotic forms of radiocarbon such as radiopharmaceuticals, these three models may not be used. Another limitation of the three proposed models is the lack of experimental data to develop the models. The clearance rates (half-times) from the body and individual organs have been studied for many carbon compounds, yet the data were not considered in the development of the

models. A more effective generic model should be based upon experimental data for known carbon compounds such that the model may be used for intakes of substances other than strictly dietary radiocarbon.

The feasibility of creating a generic biokinetic model for radiocarbon was studied by Taylor [96]. Twenty-seven different carbon-14 labelled compounds were studied by Taylor to determine the biokinetic behavior. Effective doses were calculated for many substances that had not been analyzed dosimetrically. The dose coefficient calculations made by Taylor were rough estimates used for comparison with the GCM of the ICRP. It was determined that the GCM was a significant overestimate of the dose. Also, only seven of the twenty-seven compounds were retained at a level greater than 20% seven days after administration. This suggests that a rapid clearance is occurring, and the forty day half life suggested by the ICRP is an over-simplification. The compounds were grouped by chemical form (DNA precursors, steroid-derivatives, amino acids, glycerides, etc.), but similar behavior was not observed among compounds in the individual groups. An observation was made that the effective doses calculated for [^{14}C]- CO_2 by three different biokinetic models yielded doses that varied by an order of magnitude. Based upon this and other observations, it was concluded by Taylor that doses differing by a factor of less than or approximately three are not significantly different than each other biologically or statistically. It was recommended by Taylor that the use of the GCM should be reserved for situations where ^{14}C is widely distributed throughout the environment and is present in the diet, and it should not be used for bioassay purposes.

CHAPTER 3: METHODOLOGY

3.1 Carbon Compounds in Literature

In order to create a biokinetic model for radiocarbon, the individual radiocarbon compounds were studied. As expected, many radiocarbon compounds exist as a byproduct of industry ($^{14}\text{CO}_2$ from CANDU reactors) [23], for use in medical diagnostics ([1- ^{14}C]-glycocholic acid) [29, 33, 36], and for use in industry ([1- ^{14}C]-benzene) [9, 19, 66, 88, 99]. Many radiocarbon compounds were considered, with the selection of compounds being based upon the significance of the compound and the relevant research available.

3.1.1 [1- ^{14}C]-Glycocholic acid

[1- ^{14}C]-Glycocholic acid (GCA) is used to investigate abnormal bacterial overgrowth or reduced resorption of bile acids in the small intestine [32]. The bond between the two parts of GCA, cholic acid (steroid) and glycine moiety (amino acid), is broken when GCA is exposed to bacterial enzymes. The [1- ^{14}C]-glycine is converted to $^{14}\text{CO}_2$, transported in the blood to the lungs, and exhaled. An increase in $^{14}\text{CO}_2$ in the breath indicates either an increase in the amount of deconjugating microorganisms in the small intestine, or that bile acids are not being absorbed efficiently in the small intestine and are passing down to the colon, where $^{14}\text{CO}_2$ is produced in the bacteria-rich

environment, transported in the blood, and exhaled. In the normal case, the majority of the bile salts are returned in the conjugated form to the liver via enterohepatic circulation and only a minor fraction escapes absorption.

Gunnarsson et al. developed a model for the ingestion of [1-¹⁴C]-glycocholic acid consisting of three major parts [36]. One segment modeled the conjugated compound, another segment modeled the liberated glycine moiety, and the final segment was a CO₂/bicarbonate pool. After ingestion, the conjugated bile acid is primarily absorbed by the terminal ileum during the enterohepatic cycle and becomes almost exclusively confined to the lumen of the biliary ducts, gut, and liver [39]. The bile acid undergoes enterohepatic circulation roughly six times per day.

Approximately 18% of the bile acid is deconjugated during each enterohepatic circulation, resulting in biological half life of 19h. For the normal case, a large fraction (46%) of the [1-¹⁴C]-glycine is transported through the intestinal tract rapidly ($T_{1/2} = 3$ h [11%], $T_{1/2} = 14$ h [89%]), converted to ¹⁴CO₂ by the bacteria in the colon, and transported to the bicarbonate pool to be exhaled. The residence times in the upper large intestines and the lower large intestines for the fraction excreted in feces, 7.5%, are in accordance with the ICRP gastrointestinal model [44]. It is assumed that a significant fraction, 44%, of the glycine not metabolized to CO₂ is transported in the blood from the liver, and incorporated into tissue proteins, where glycine is metabolized to CO₂ by tissue enzymes and transferred to the bicarbonate pool, $T_{1/2} = 6$ days (70%) and $T_{1/2} = 77$ days (30%). The distribution of glycine within the tissue proteins should be according to protein contents in various organs from ICRP 23 [43]. A small fraction, 2.5%, of the ¹⁴C

is excreted in the urine according to the ICRP bladder emptying model [47]. The structure of the model is presented in Figure 3.1.

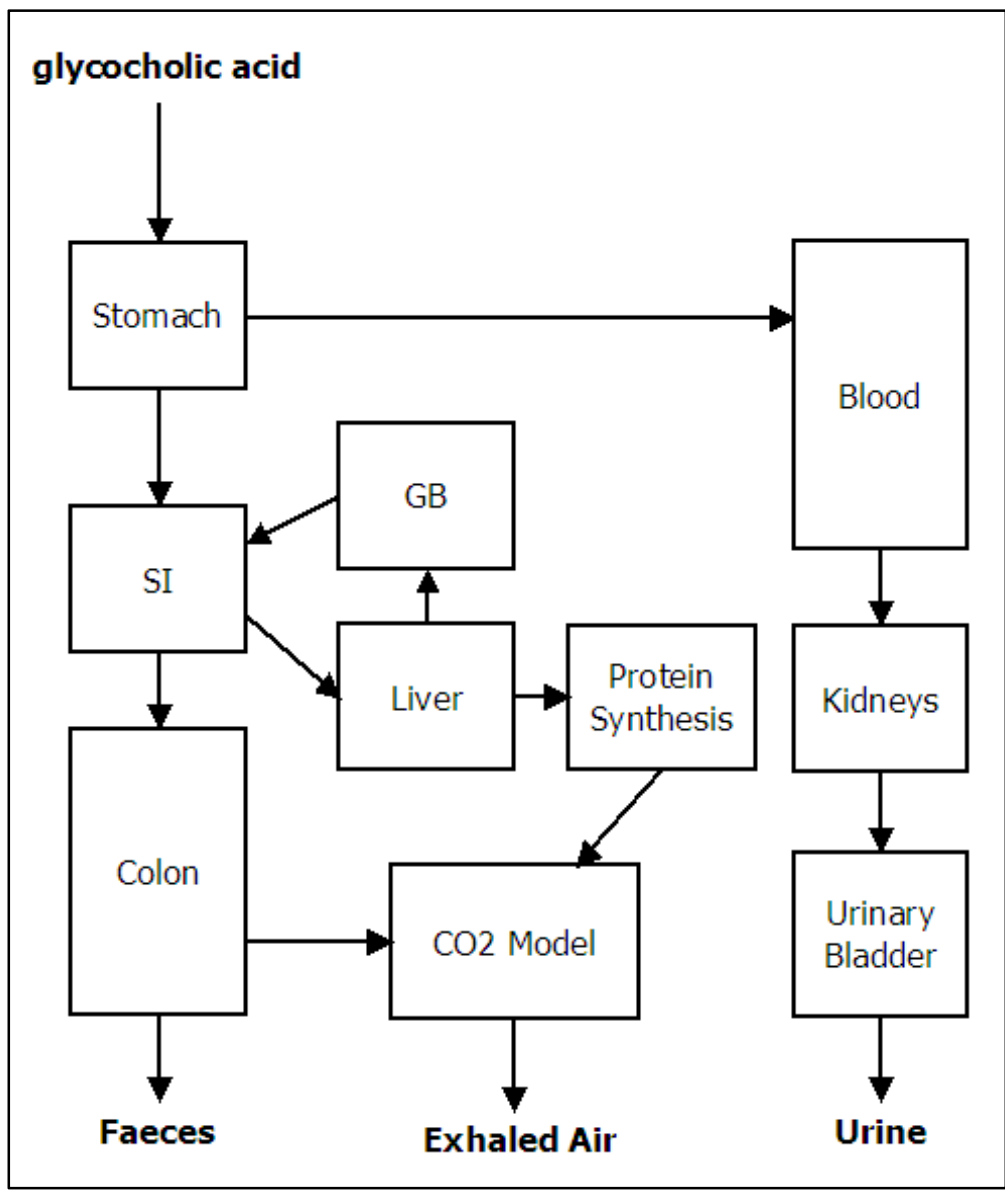


Figure 3.1 Model structure for the ingestion of [1-14C]-glycocholic acid.

3.1.2 D-[U-¹⁴C]-xylose

Xylose is a monosaccharide used for the diagnosis of abnormal intestinal bacterial flora. It was developed to avoid false positive results from ¹⁴C-GCA breath tests [64]. The advantage of xylose over GCA is that it is primarily absorbed in the proximal half of the small intestine, restricting the amount of xylose reaching the bacteria-rich colon. Xylose is mostly excreted unchanged in the urine after being absorbed in the proximal part of the small intestine, but if there are bacteria present in the small intestine, the xylose is metabolized into CO₂ and ultimately exhaled [13]. Therefore, the presence of an abnormal amount of intestinal bacterial flora will result in an increase in the exhalation of ¹⁴CO₂.

Gunnarsson et al. developed a model for the ingestion of D-[U-¹⁴C]-xylose [36]. Following ingestion, the xylose is transported from the stomach to the small intestines where a major fraction is absorbed and transported to the plasma and extra cellular fluid. Approximately 70% of the total xylose elimination is found in the urine ($T_{1/2} = 2.5$ h). The remaining 30% is eliminated via exhalation. Of this 30%, 40% is rapidly exhaled with $T_{1/2} = 1.1$ h (42%) and $T_{1/2} = 3$ days (58%) after being metabolized in the liver. The remaining 60% becomes incorporated in adipose tissue and metabolized to ¹⁴CO₂ to be exhaled ($T_{1/2} = 60$ days). The structure of the D-[U-¹⁴C]-xylose ingestion model is shown in Figure 3.2.

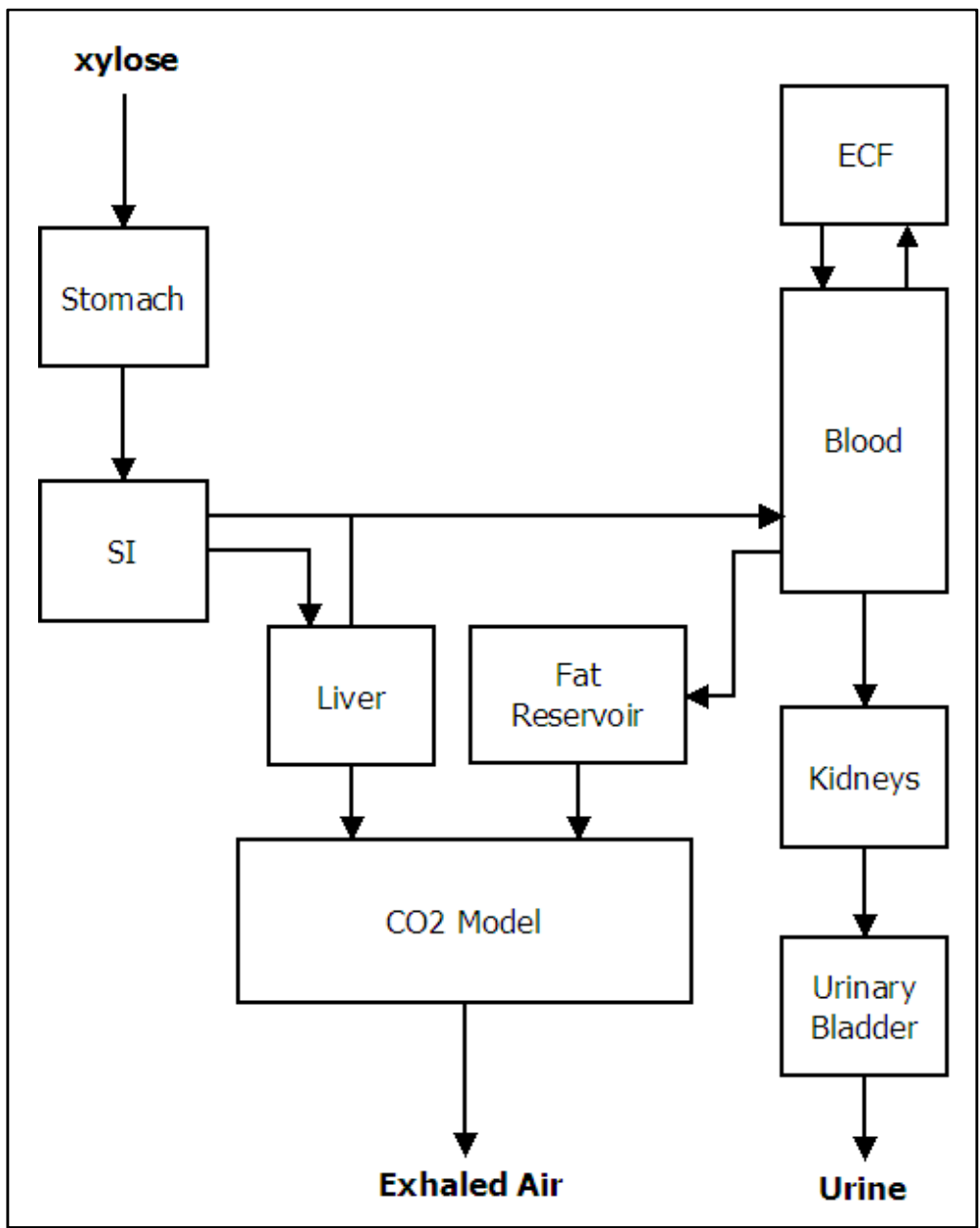


Figure 3.2 Model structure for the ingestion of D-[U-14C]-xylose.

3.1.3 Glycerol tri-[1-¹⁴C]-oleate (triolein)

Glycerol tri[1-¹⁴C]oleate (triolein) is a triglyceride with a ¹⁴C-label on the first carboxyl group. When triolein reaches the intestine after ingestion, it is primarily hydrolyzed in the jejunum via pancreatic and intestinal lipases [81]. A small amount of hydrolysis also occurs in the stomach. After partial hydrolysis in the jejunum, the fat is introduced into the blood as chylomicrons after absorption through lymphatic vessels. A great amount of liberated free fatty acid is converted to ¹⁴CO₂ by oxidation in the liver. The CO₂ is eventually exhaled. An individual with fat malabsorption will exhale a smaller fraction of the administered activity and excrete a larger fraction in the feces as a result of less free fatty acids reaching the liver [77].

Gunnarsson et al. studied the biokinetics of ¹⁴C-triolein by performing breath tests on human subjects [35, 91, 92]. The biokinetic model used by Gunnarsson was based upon kinetic data from the human subjects and the ICRP model of ¹⁴C-labelled neutral fat [51] and is displayed in Figure 3.3. After ingestion, the triolein rapidly passes through the stomach into the small intestine where 70% of the ¹⁴C-triolein is transported to the liver following hydrolysis. In the liver, 28% of the fat compound is metabolized to ¹⁴CO₂ (T_{1/2} = 1 h) and transported to the bicarbonate pool. The remaining 42% becomes incorporated in adipose tissue (85%) (a₁=57%, T_{1/2} = 2 days; a₂ = 43%, T_{1/2} = 137-620 days), muscle (10%) (T_{1/2} = 2 days), and other organs (5%) (T_{1/2} = 137-620 days), where the triglycerides are oxidized and transferred to the bicarbonate pool. The kidney-bladder system receives 25% of the administered activity (T_{1/2} = 4 h). The remaining 5% of the

administered activity passes through the GI tract and is excreted in the feces according to the gastrointestinal model.

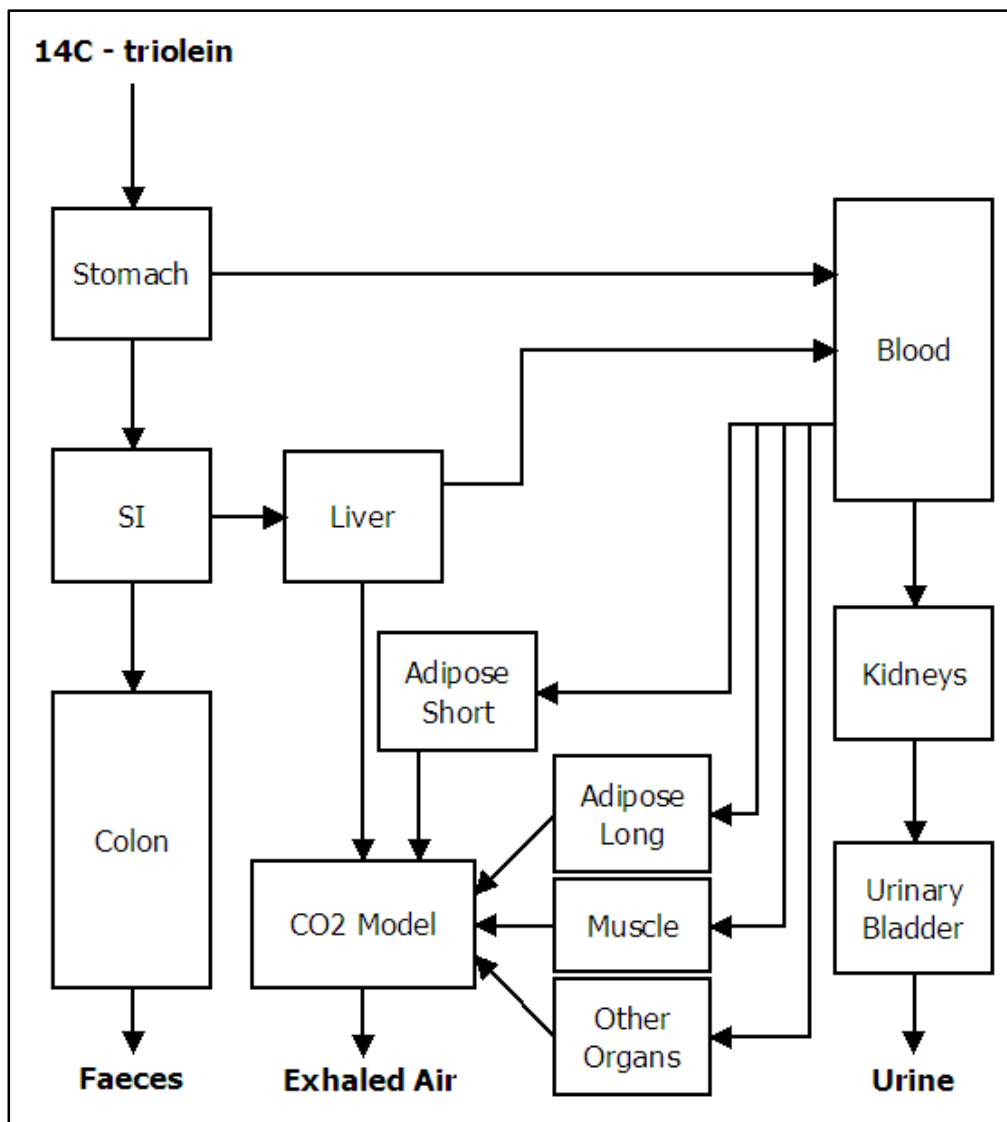


Figure 3.3 Biokinetic model structure for the ingestion of glycerol tri[1-14C]oleate.

3.1.4 [¹⁴C]-Urea

¹⁴C urea (carbamide, H₂N¹⁴CONH₂) is the main end product in the human catabolism of proteins, polypeptides, amino acids, and other nitrogen-containing substances. It is water-soluble and distributes rapidly into the total body water [57, 58]. ¹⁴C urea is used for the diagnosis of *Helicobacter pylori* (*Hp*) infection in the stomach. *Hp* bacteria produce urease, which metabolizes urea, producing CO₂. In an *Hp* negative individual, the urea is rapidly absorbed unchanged into body water, not producing any excessive CO₂. The urea breath test is a diagnostic method to test for *Hp* infection by administering a cocktail of ¹⁴C-labelled urea to the patient orally [71]. Exhaled breath samples are taken 5, 10, 15, and 20 minutes after administration to determine if ¹⁴CO₂ levels are above a predefined threshold value.

In the normal case, ¹⁴C-urea is completely absorbed in the stomach with a half-life of 5 minutes. In the *Hp* positive case, it is assumed that 65% is immediately converted into ¹⁴CO₂ and treated according to the dosimetric model for ¹⁴CO₂/H¹⁴CO₃. The remaining 35% are absorbed by the stomach as in the normal case. The urea absorbed by the stomach is rapidly distributed in the total body water. Eighty percent of the urea in the total body water is excreted by the kidneys with a half-time of 6 hours, and 20% is rapidly dissociated in the same way as intravenously administered urea to ammonia and carbon dioxide and treated according to the dosimetric model for CO₂/HCO₃. The structure of the biokinetic model is presented in Figure 3.4.

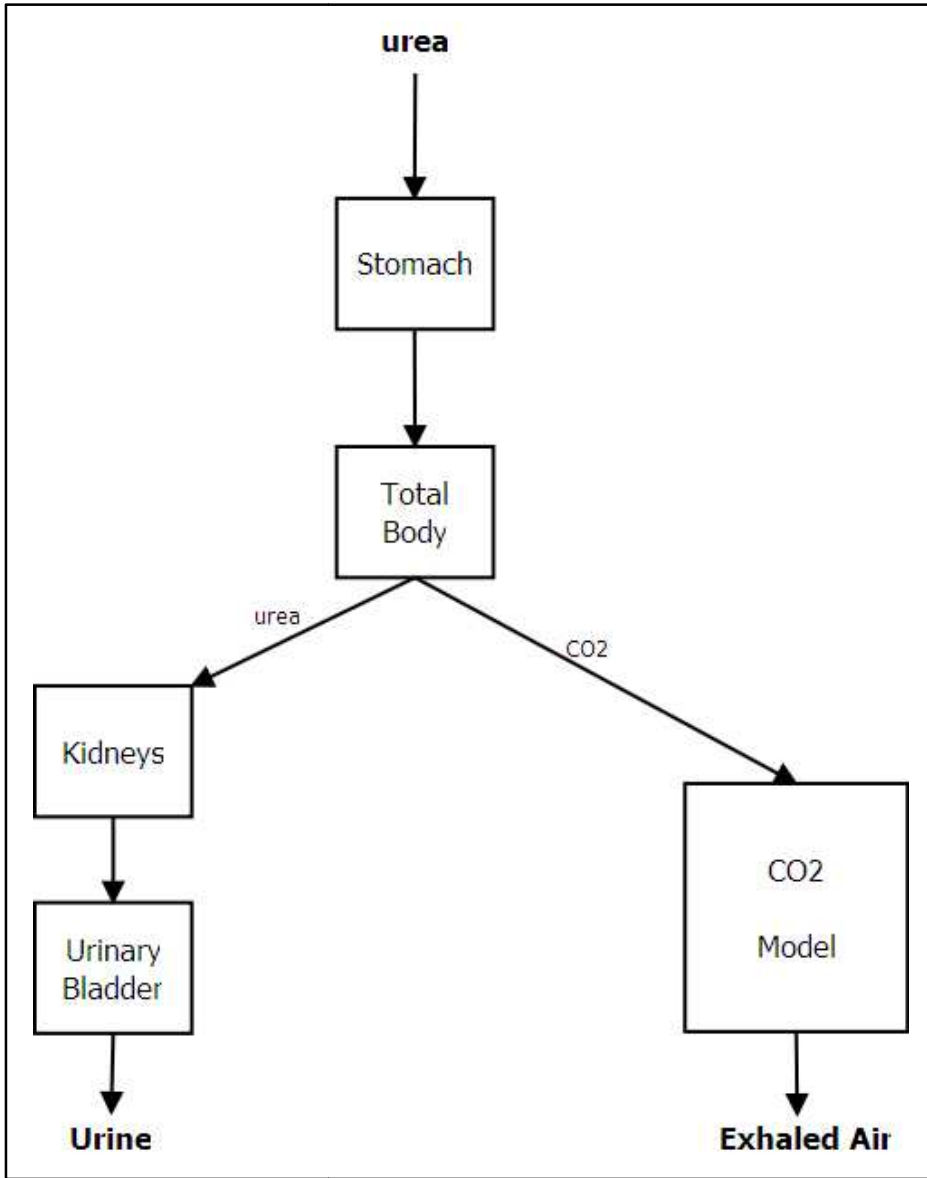


Figure 3.4 Biokinetic model structure for urea.

3.1.5 [1-¹⁴C]-Benzene

Travis et al. developed a model for [¹⁴C]-benzene consisting of eight compartments [99]. After inhalation of benzene, it is immediately deposited into a blood pool which exchanges activity with five compartments: adipose tissue, a muscle group, an organ group, bone marrow, and liver. The bone marrow and liver compartments feed a metabolite compartment, which is essentially a blood compartment, circulating the metabolites through the body. The bone marrow and liver compartments are governed by Michaelis-Menten kinetics such that at high concentrations of activity, the excretion via urine and breath is approximately equal, and at low concentrations of activity, the excretion via urine is approximately 90%. The water soluble metabolites empty into the urinary bladder after being removed from the blood by the kidneys. The transfer coefficients, the fractional transfer per unit time from one compartment to another, between compartments are presented in Table 3.1 for a case of high exposure (800 ppm benzene) and the model structure is shown in Figure 3.5 [66].

Table 3.1 Transfer coefficients for biokinetic model for inhalation of [1-¹⁴C]-benzene.

Compartment	Transfer coefficient (d ⁻¹)
Blood to Adipose Tissue	85.85
Blood to Muscle Group	377.72
Blood to Organ Group	755.45
Blood to Bone Marrow	66.96
Blood to Liver	429.23
Blood to Exhaled Air	187.11
Adipose Tissue to Blood	0.61
Muscle Group to Blood	24.19
Organ Group to Blood	748.25
Bone Marrow to Blood	7.77
Bone Marrow to Metabolite	1.78
Liver to Blood	817.58
Liver to Metabolite	729.42
Metabolite to Urine	4.32

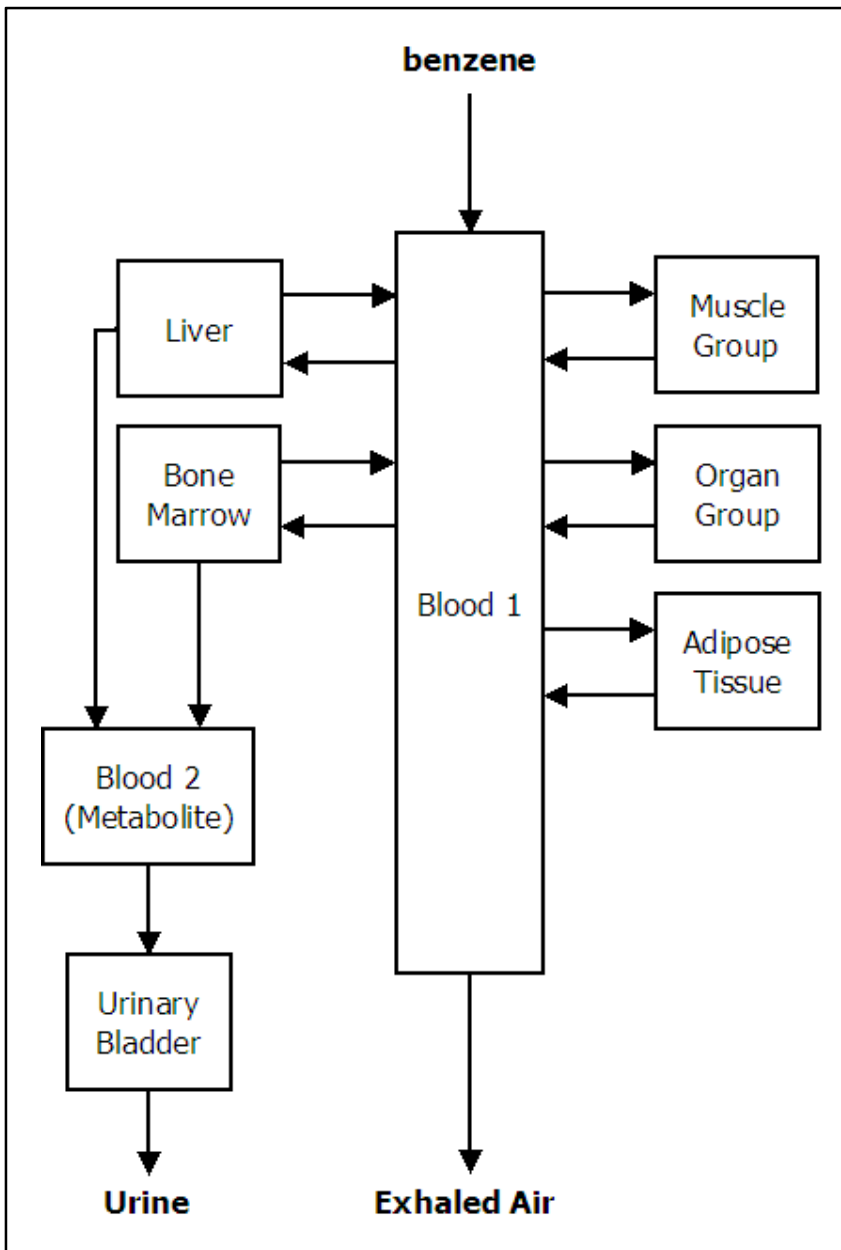


Figure 3.5 Structure for the model of [14C]-benzene inhaled.

3.1.6 [¹⁴C]-CO₂/¹⁴C-bicarbonate

Inhaled carbon dioxide (CO₂) is transferred rapidly across the alveolar membrane into blood [37]. Carbon dioxide is also formed in the body during the metabolism of organic substances. Because most of the absorbed or internally produced carbon dioxide is converted to bicarbonate after entering blood, data from metabolic studies involving intravenous injection of [¹⁴C]bicarbonate provide information on the systemic biokinetics of carbon inhaled as CO₂.

Data for intravenously injected [¹⁴C]bicarbonate were used in the development of the model for inhaled CO₂ introduced in ICRP Publications 30 [45] and applied in several subsequent ICRP documents on occupational or environmental intake of radionuclides. According to that model, inhaled carbon is rapidly and completely absorbed from the lungs and distributed uniformly throughout the body. Retention, R(t), is described by the sum of three exponential terms:

$$R(t)=0.18e^{-\frac{0.693 t}{5}}+0.81e^{-\frac{0.693 t}{60}}+0.01e^{-\frac{0.693 t}{60,000}} \quad \text{[Equation 3.1]}$$

where t is in minutes. The first two terms are based on a two-exponential curve fit to data of Winchell et al. [104] on retention of ¹⁴C in 13 normal human subjects over the first 120 min after intravenous injection with [¹⁴C]bicarbonate. The third term was added to represent a small component of relatively long-term retention observed in laboratory

animals administered $^{14}\text{CO}_2$ by inhalation. The coefficient of the third term, 0.01, is based on the interpretation that the two short-term components of retention identified in the subjects of Winchell and coworkers accounted for at least 99% of the administered activity. The removal half-time associated with the third term (~40 d) is the estimated effective half-time for dietary carbon in a typical adult human, i.e., assuming the body's carbon behaves as a single well-mixed pool.

ICRP Publication 80 [57, 58], which addresses doses from radiopharmaceuticals, describes a recycling model for ^{14}C as carbon dioxide or bicarbonate formed in the body after administration of ^{14}C -urea (Figure 3.6). This is an extension of a recycling model of Winchell and coworkers [104] developed from the same [^{14}C]bicarbonate injection data used by the authors of ICRP Publication 30 to derive the model for inhaled carbon dioxide. Winchell's model was modified by assignment of a removal half-time of 1000 h to Winchell's "relatively fixed" carbon compartment, based on the long-term half-time used in ICRP Publication 30 (Equation 3.1) and by addition of bone compartments with low uptake and with removal half-times based on bone turnover. Rates of inflow into the bone compartments were chosen so that realistic carbonate or bicarbonate pool sizes were reached during a lifetime.

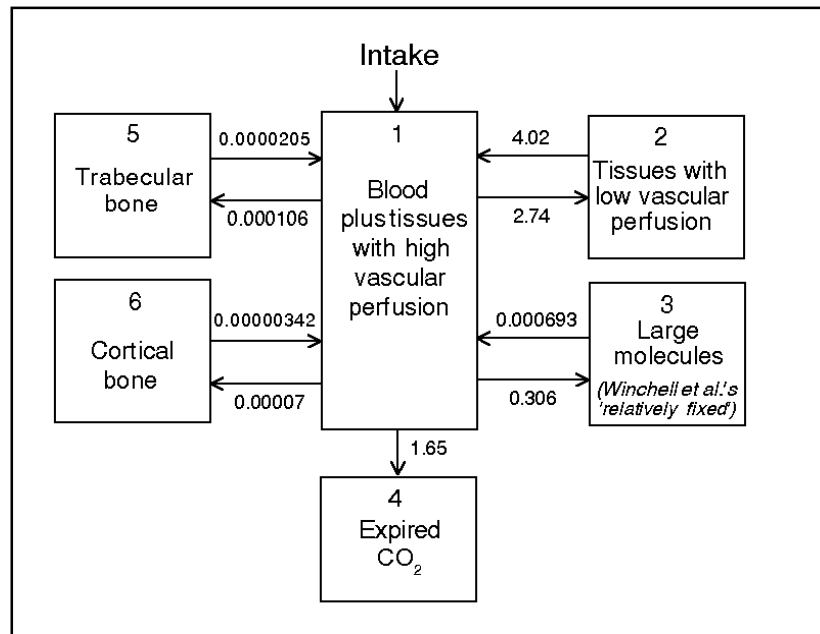


Figure 3.6 Model for CO₂/bicarbonate formed in body after intake of urea (ICRP 80)

Leggett [69] proposed a more detailed recycling biokinetic model for systemic radiocarbon taken into the body as carbon dioxide or bicarbonate. Parameter values describing retention and excretion of activity during the first few weeks after administration were based on studies of the fate of radiocarbon in human subjects after intake of labeled bicarbonate or carbon dioxide. Data from laboratory animals given labeled bicarbonate, carbon dioxide, or carbonate were used to model the tissue distribution and the long-term retention of carbon. The model includes a central blood compartment that exchanges carbon with six soft tissue compartments and five bone compartments representing different phases of retention as indicated by the experimental data. In addition to loss of label through exhalation of CO₂, the model depicts small losses in urine and feces and through skin. The model provides a reasonably close reproduction of reported biokinetic data from biokinetic studies of human subjects

exposed to labeled bicarbonate or carbon dioxide. The model was designed to yield higher total-body retention and bone retention of activity than observed in laboratory animals, in view of the relatively high metabolic rates and bone turnover rates in the studied animal species.

A variation of the model proposed by Leggett was applied for use in an upcoming ICRP report [70] to radiocarbon taken into the body as carbon dioxide or bicarbonate. The structure of the modified model is shown in Figure 3.7. Parameter values are listed in Table 3.2. The modifications were made to bring the model into line with the generic modeling scheme used in this report, simplify implementation of the model by reduction of the total numbers of compartments and pathways, and improve the accuracy of the predicted urinary excretion rate at times remote from intake by including additional phases of transfer from soft tissues to the urinary excretion pathway. The modified model adds a blood compartment (Blood 2) and pathways from soft tissues to the urinary bladder contents via Blood 2 that account for a delay in excretion of a portion of the activity appearing in urine. The modified model simplifies the original model overall by eliminating compartments and pathways depicting rapid exchange of activity between blood and peripheral compartments. Those features of the original model do not appear to be of much practical importance in radiation protection.

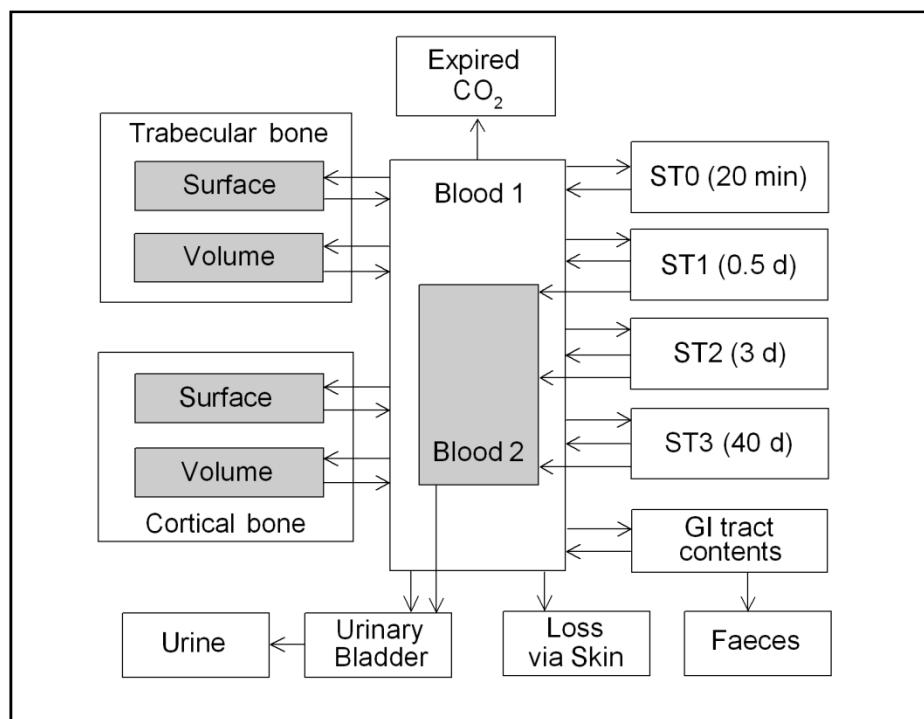


Figure 3.7 Systemic model for carbon taken into the body as CO₂/bicarbonate.

In the present model (i.e., the model defined in Figure 3.7 and Table 3.2), absorbed carbon is assigned to Blood 1. Activity leaves Blood 1 at the rate 100 d^{-1} ($T_{1/2} = 10 \text{ min}$), with 60% of the outflow assigned to ST0, 1.8% to ST1, 0.3% to ST2, 0.44% to ST3, 0.15% to bone surface, 0.01% to bone volume, 36.2% to excreta through exhalation, 0.3% to excreta via skin, 0.65% to the bladder contents, and 0.15% to the right colon contents. Removal half-times from ST0, ST1, ST2, and ST3 are 20 min, 0.5 d, 3 d, and 40 d, respectively. It is assumed that 4% of outflow from ST1, ST2, and ST3 enters Blood 2 and all other outflow from the four soft tissue compartments returns to Blood 1. Activity transfers from Blood 2 to the urinary bladder contents at the rate 1000 d^{-1} ($T_{1/2} = 1 \text{ min}$). Based on estimates of the relative masses of Trabecular and cortical bone replaced per unit time in an adult human, 60% of carbon entering bone is assigned to

Trabecular bone and 40% is assigned to cortical bone. The Trabecular and cortical bone surface compartments are assumed to lose carbon to Blood 1 with a half-time of 40 d. The bone volume compartments are assumed to lose carbon to Blood 1 at the rate of bone turnover, which differs for Trabecular and cortical bone.

Table 3.2 Transfer coefficients for systemic model of carbon dioxide or bicarbonate

From	To	Transfer coefficient (d ⁻¹)
Blood 1	Excreta (exhalation)	36.2
Blood 1	Excreta (via skin)	0.3
Blood 1	Urinary bladder contents	0.65
Blood 1	Right colon contents	0.15
Blood 1	ST0	60
Blood 1	ST1	1.8
Blood 1	ST2	0.3
Blood 1	ST3	0.44
Blood 1	Trabecular bone surface	0.09
Blood 1	Cortical bone surface	0.06
Blood 1	Trabecular bone volume	0.006
Blood 1	Cortical bone volume	0.004
ST0	Blood 1	49.91
ST1	Blood 1	1.331
ST2	Blood 1	0.2218
ST3	Blood 1	0.01664
ST1	Blood 2	0.05545
ST2	Blood 2	0.009242
ST3	Blood 2	0.0006931
Blood 2	Urinary bladder contents	1000
Trabecular bone surface	Blood 1	0.01733
Cortical bone surface	Blood 1	0.01733
Trabecular bone volume	Blood 1	0.0004932

Total-body retention of carbon following acute input of carbon dioxide or bicarbonate into blood based on the present model agrees closely with predictions based on the original model [69]. Also, in agreement with the original model, the present model predicts that exhalation, urinary excretion, fecal excretion, and loss through skin accounts for 96.8%, 2%, 0.4%, and 0.8%, respectively, of the total loss of activity from the body over an extended period. One difference in predictions of the two models is that the present model predicts slower accumulation of activity in bone than the original model, but the two models predict similar levels of activity in bone beyond a few days after acute input of activity to blood. For example, the present model predicts that bone contains 0.41% of intake at 1 d, 0.36% at 10 d, and 0.098% at 100 d after intake, compared with predictions of 0.89% at 1 d, 0.38% at 10 d, and 0.096% at 100 d based on the original model.

3.1.7 [¹⁴C]-Methane

The dosimetric implications of inhaling methane gas were examined by Phipps *et al.* [80]. In the absence of other experimental information they made the conservative assumption that 1% of the methane was metabolized. Recent data of Carlisle *et al.* [10] suggest this to be an overestimate, and that a value of 0.1% is more likely. Dougherty *et al.* [20] estimated that approximately 0.3% of infused methane was converted to carbon dioxide in sheep. The available data indicate that radioactive carbon-labelled methane is oxidized to carbon dioxide, but the possibility of some activity being incorporated into

other organic molecules cannot be excluded. In an addendum to ICRP Publication 72 [55] a conservative assumption was made that one half of the metabolized fraction is retained as carbon dioxide and one half as organic carbon. The committed effective dose coefficient was given as $2.9\text{E-}12 \text{ Sv Bq}^{-1}$ [58].

3.1.8 [^{14}C]-Carbon monoxide

Carbon monoxide (CO) is a potent asphyxiant at high concentrations [12]. The distribution and retention of [^{14}C]-carbon monoxide has been studied extensively. Carbon monoxide readily diffuses across the membranes of the alveolar interstitial region of the lung [14]. ICRP Publication 30 [44] suggests that upon the inhalation of [^{14}C]-CO, 0.4 is instantaneously bound to hemoglobin ($T_{1/2} = 200 \text{ min}$) and 0.6 is instantly exhaled. Peterson and Stewart estimated the biological half-life of CO in the blood to be from 150 to 200 minutes [79]. Therefore, the carbon monoxide bound to hemoglobin is assumed to be uniformly distributed throughout all organs and tissues and retained with a biological half-time of 200 minutes. Carbon monoxide is assumed to be Class SR-1 (40% deposition) with Type V clearance. The corresponding effective dose coefficient calculated by the ICRP is $8.0\text{E-}13 \text{ Sv Bq}^{-1}$ [55].

3.1.9 Other radiocarbon compounds

Several other radiocarbon compounds have been researched, but in less detail than the eight compounds already presented. A list of some other radiocarbon compounds, the

uptake pathway, and estimates of dose coefficients are presented in Table 3.3. Detailed models are not available for these compounds, therefore many assumptions were made by the authors in calculating the dose coefficients.

Table 3.3 The effective dose coefficients of some other radiocarbon compounds

Compound	Intake	$E(\text{Sv Bq}^{-1})$
Ba[¹⁴ C]-Carbonate [65]	Inhalation	2.0E-10
K[1- ¹⁴ C]-Cyanide [rat] [16]	Intubation	4.6E-11
[1- ¹⁴ C]-Methanol [rat] [16]	IV	5.1E-11
[2- ¹⁴ C]-Acetate [17]	IV	4.6E-11
[¹⁴ C(U)]-Glucose [1, 24, 73]	IV	2.1E-10
[2- ¹⁴ C]-Glycine [5, 6, 23, 23]	IV	3.3E-10
[1- ¹⁴ C]-Alanine [89]	IV	1.9E-10
[4- ¹⁴ C]-Cholesterol [42]	IV	3.0E-10
[4- ¹⁴ C]-Testosterone [25,26]	IV	8.2E-11
[16- ¹⁴ C]-Estrone – [16- ¹⁴ C]-Estradiol-17β	IV [2, 3, 87]	3.4E-11
[4- ¹⁴ C]-Corticosterone [41]	IV	9.3E-12
[4- ¹⁴ C]-Cortisol [41, 76]	IV	9.8E-12
[¹⁴ C]-Inulin [47]	IV	8.2E-12
	Ingestion	2.9E-11
[2-Acetate- ¹⁴ C]-DTPA [90]	Inhalation	8.8E-11
	IV	8.7E-12
[¹⁴ C]-Nitrobenzene [rat] [18]	Intubation	6.3E-11
[¹⁴ C]-Delmopinol [22]	Ingestion	2.9E-11
[¹⁴ C]-Dexloxiglumide [101]	Ingestion	2.5E-10

3.2 Grouping of carbon compounds

The dose coefficients of the previously listed radiocarbon compounds range from the order of 10^{-13} (for carbon monoxide) to 10^{-10} Sv Bq⁻¹ (for Ba-carbonate and others). Due to this wide variation in dose coefficients, it was considered that the compounds should be grouped into classes denoted by a common characteristic: dose coefficient, pathway of uptake, or chemical form.

The first type of grouping considered was a grouping by dose coefficient. A scatter plot ranking the carbon compounds by dose coefficient was created (Figure 3.8), but carbon monoxide, methane, and carbon dioxide, three well-known carbon gasses are not included in the plot. Three distinctive groups are revealed when sorting in this manner.

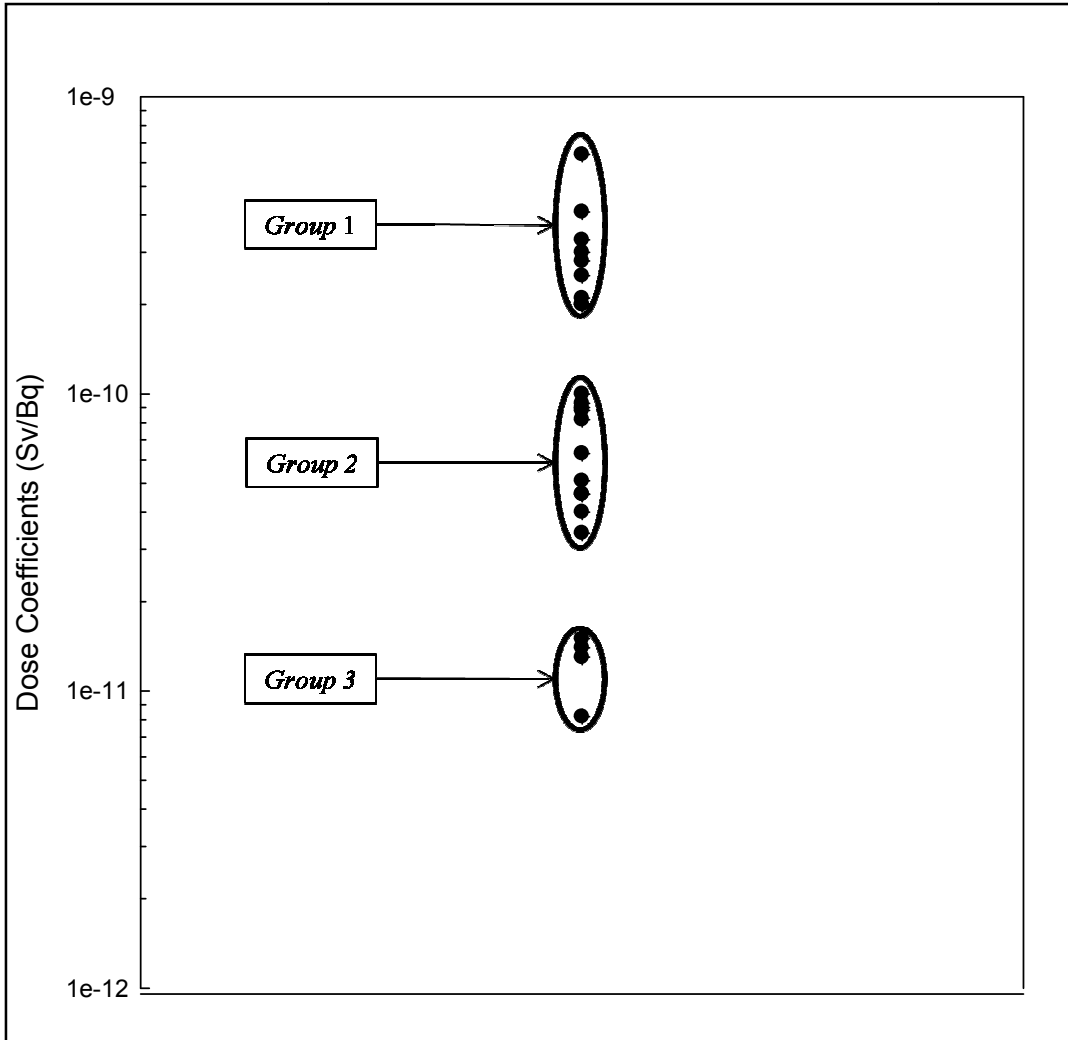


Figure 3.8 Scatter plot of dose coefficients

To determine if the carbon compounds within these three groups share common biokinetic or chemical traits, the compounds from “Group 2” ($3.4\text{E-}11$ to $1\text{E-}10$ Sv Bq⁻¹) were studied. The compounds in group two did not share a common path of uptake and do not share a common chemical form. For example, [1-¹⁴C]-urea is studied for the case of ingestion, but [4-¹⁴C]-testosterone is studied for the case of injection. [4-¹⁴C]-cortisol is a steroid-derivative, and [¹⁴C]-xylose is a monosaccharide. The compounds in Group 2 are not similar on a biokinetic basis either. [16-¹⁴C]-estrone-[16-¹⁴C]-estradiol-17 β has a retention of approximately 20% a week following prompt intake while [¹⁴C]-nitrobenzene has a retention of approximately 6% a week after intake. Group 1 and Group 3 were also studied, and they did not share any biokinetic or chemical traits.

Since no similarities were revealed by sorting the compounds, the pathway of uptake and the chemical forms should be considered as a possible trait that may determine how the human body treats a radiocarbon compound. Considering only the inhaled compounds, the dose coefficient fluctuates from a low value of $8.0\text{E-}13$ Sv Bq⁻¹ to a high value of $2.0\text{E-}10$ Sv Bq⁻¹ for Ba[¹⁴C]-carbonate, a factor of 4,000 difference. The manner by which the compound is deposited in the body is not a determining factor of the dose coefficient or biokinetics considering such a large variation in dose coefficients.

The final category by which the compounds were sorted in attempt to expose similar biokinetics was chemical characteristics. Taylor has already attempted to sort the most studied radiocarbon compounds using this approach, but it was not successful. An example of a chemical grouping used by Taylor [96] is presented in Table 3.4. The dose

coefficient varies from a value of $9.3\text{E-}12$ to $4.0\text{E-}10$ Sv Bq⁻¹ and the retention at 7 days ranges from 55% to less than 10%.

Table 3.4 Retention and Dose Coefficients of some radiocarbon steroid-derivatives

Compound	Intake	Retention at 7d (%)	E (Sv Bq ⁻¹)
[4- ¹⁴ C]-cholesterol	IV	~55	3.0E-10
[1- ¹⁴ C]-glycocholic acid	Ingestion	~35	4.0E-10
[4- ¹⁴ C]-testosterone	IV	<20	8.2E-11
[16- ¹⁴ C]-estrone-[16- ¹⁴ C]-estradiol-17β	IV	<20	4.5E-11
[4- ¹⁴ C]-corticosterone	IV	~10	9.3E-12
[4- ¹⁴ C]-cortisol	IV	<10	9.8E-12

Similar biokinetic behaviors were not uncovered by any of the attempts at grouping the compounds by common characteristics. The inability to reveal similar biokinetic behaviors by organizing the compounds into groups is a product of the wide variety of radiocarbon-containing compounds.

3.3 Generic radiocarbon model development

The manner in which radiocarbon compounds are processed by the human body is dictated by the chemical form of the radiocarbon. With various chemical forms of carbon in existence, the biokinetics of the radiocarbon varies greatly among all compounds. Excretion data and common anatomical characteristics were the primary source of information used in the development of an improved generic radiocarbon model.

3.3.1 Development of Model Structure

The three major pathways of excretion for the radiocarbon compounds considered in this paper are breath (exhalation), urine, and feces. For the compounds in Table 3.3, the urinary excretion ranges from 1 to 100% (rounded average of 60%), the breath excretion ranges from 0 to 95% (rounded average of 25%), and the fecal excretion ranges from 0 to 99% (rounded average of 15%). According to Taylor [95, 97], the pathway of excretion and the rate at which a compound is eliminated from the human body have a correlation to the dose coefficient. Therefore, the large range in the effective dose coefficients for the compounds in Table 3.3 are a product of the widely varying excretion pathways.

The excretion of radiocarbon from the human body can be described by a 3 – or less – component exponential with a major short term component, an intermediate component, and a long term component. The GCM of the ICRP has a single component elimination, which is described by a one component exponential elimination rate. In order to account for the multi-half-life excretion rate, multiple compartments are necessary. To determine these compartments, common anatomical features and excretion data were observed from the previously developed models.

The organs through which the compounds pass vary among all compounds. Some compounds may pass through the liver or gall bladder while others may not. A compartment that is utilized frequently in biokinetic modeling for combining many organs into one “pool” is the “Other” compartment. All organs besides those pre-defined by a biokinetic model are accounted for in the “Other” compartment. For modeling a

generic radiocarbon-containing substance, the “Other” compartment would be useful because the affected organs vary for each compound, and the “Other” compartment will represent the organs that are different for each compound (liver, kidneys, spleen, etc.). The disadvantage of using an “Other” compartment is that the model will not be as physiologically accurate modeling the manner in which the human body processes an intake of radiocarbon. For this reason, it is discouraged to use a compartment that generalizes an organ or tissue, such as the “Other” compartment, when modeling specific compounds. But for creating a generic model, the encapsulating nature of the “Other” compartment is preferred because it will be able to represent any organ that may be burdened by the chemical after it is deposited within the human body.

When considering any carbon substance, carbon dioxide must be considered because of its vital role in critical biochemical processes. CO₂ is a critical component in cellular respiration and pH regulation within the human body. According to the Bohr effect, as the amount of carbon dioxide increases, more H⁺ are formed and the pH will decrease. Therefore, a lower pH in the blood is often the product of increased carbon dioxide concentration. The increase in carbon dioxide concentration also suggests that a tissue is more active and requires more oxygen. As a response, the smooth muscles will dilate to increase oxygen flow to the muscles because of the increase in carbon dioxide concentration, making carbon dioxide a negative regulator of smooth muscle dilation. This is also observed in the lungs. When alveolar CO₂ levels are low, the smooth muscle will constrict, but if CO₂ levels are high, the smooth muscle will dilate.

The biokinetic models presented in sections 3.1.1-3.1.5 and 3.1.7 all contain a carbon dioxide pool because of the production of CO₂ as a metabolic side-product of

processing the compound. In addition, models for glycine and some of the models proposed for dietary carbon also contain a CO₂ compartment. Due to the vital role of CO₂ in the human body metabolism and the consideration of CO₂ in previous radiocarbon models, a CO₂ compartment was considered in the development of a generic model.

Another common feature in many carbon models is the long term retention of radiocarbon in the adipose tissue. To represent the long term component of the elimination of carbon from the human body, many models divert a portion of the internalized radiocarbon to an adipose tissue compartment that represents long term retention. It was mentioned by Richardson [86] that the difference in carbon-14 doses between men and women is due to the carbon saturation in adipose tissue, and in the current ICRP dosimetric construct, the activity burden in adipose tissue is “lost dose.” A few examples of models that consider adipose tissue for long term retention of radiocarbon are glycocholic acid, xylose, triolein, methanol (rat study), and cyanide (rat study). The adipose tissue compartment will represent the long term retention component that is expressed in many radiocarbon excretion data. A half-life of 100 days was given to the adipose tissue compartment, based upon a rounded average of the available data.

In addition, an alimentary tract must be considered. All ingested substances or inhaled particulates will be swallowed and deposited in the alimentary tract beginning with the stomach, proceeding to the small intestines, and finally the colon to be excreted as feces. The alimentary tract used in the generic model is based upon the ICRP 30 GI model [45], but with the upper large intestines and lower large intestines combined into a single “Colon” compartment so that the model may be used with the updated version of the Human Alimentary Tract Model (HATM). The small intestines of the alimentary

tract will exchange with the blood, and may be deposited into the Other compartment, which may represent the liver and gall bladder. This transfer may be related to the transfer that occurs between the small intestines and the liver via the hepatic portal vein. Upon leaving the Other compartment, a portion may be metabolized, creating $^{14}\text{CO}_2$ as a by-product, or it may circulate into the Colon, enterohepatic circulation, to be ultimately excreted into the feces.

The final element of the generic model that must be considered is the kidney-bladder component. For this generic model, the kidneys are accounted for in the Other compartment, therefore only a urinary bladder is necessary. The kidney-bladder model is based upon the model presented in ICRP 53 [47]. The source which feeds the kidneys and urinary bladder is a blood pool. The blood pool is the main transfer compartment that feeds the urinary bladder and other compartments. The fractional excretion and rate of excretion are highly dependent upon the transfer rates to and from the blood compartment. The manner in which those transfer rates were chosen will be discussed in the section 3.4. The generic model structure is presented in Figure 3.9. The “Other” and “Adipose Tissue” compartments are represented in the figure as “Systemic Tissue (Short Term)” and “Systemic Tissue (Long Term)” respectively. The reason for renaming the compartments in this manner is so that the dosimetric considerations of the tissues could be altered according to the preferences of the user. For instance, the short term systemic tissue may be modeled as “Other” and the long term may be modeled as “Adipose Tissue,” but if a higher, more conservative effective dose coefficient is wanted, the long term compartment may be modeled as “Other,” as well. The dosimetric implications of the tissue choices will be considered in section 3.4.

For the case of ingestion, the compound is deposited in the stomach and is treated according to the ICRP gastrointestinal model with an f_1 value of 0.99. The portion of the compound in the blood pool is transported to the urinary bladder to be excreted as urine and to the “Other” compartment. The Other compartment metabolizes a portion of the compound to CO_2 to be deposited into the bicarbonate pool, transports a portion of the compound to the lower large intestines, and transports a final portion back into the blood pool. The portion which is transported into the Colon will be further processed and excreted as feces. The portion deposited in the bicarbonate pool will be treated according to the CO_2 /bicarbonate model developed by Leggett.

For the case of inhalation, the compound enters the human respiratory tract model (HRTM) and is transported to the stomach and blood pool to be treated as described above [52, 60].

If a radiocarbon compound is introduced into the body via a wound or intravenous injection, it will be deposited directly into the blood pool to be treated as described above.

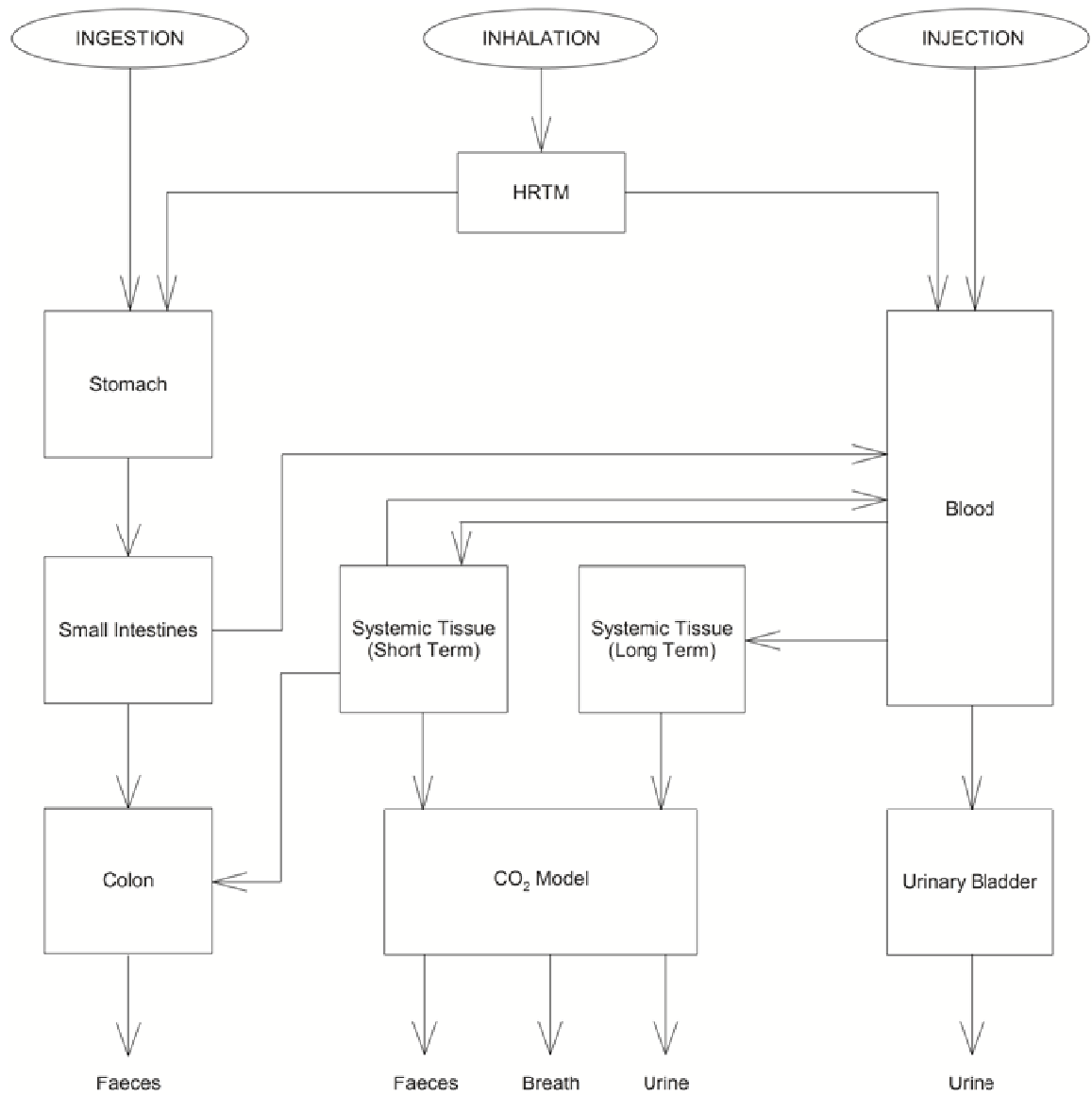


Figure 3.9 Generic Radiocarbon Model Structure.

The transfer coefficients in Figure 3.9 not previously defined are: Blood to Systemic (Short), Blood to Urinary Bladder, Systemic (Short) to Blood, Systemic (Short) to CO₂, Systemic (Short) to ULI, and Blood to Systemic (Long). The rate of excretion and the excretion pattern (fraction in feces, urine, and breath) are dictated by these systemic tissue transfer coefficients. The urinary excretion rates for some of the compounds in Table 3.3 are listed in Table 3.5. The fecal and breath excretion rates are not readily available for a significant portion of the compounds in Table 3.3, therefore only the renal excretion profile can be considered. If more data become available for fecal and breath excretion, the model can be further improved.

Table 3.5 Urinary excretion rates for various carbon compounds

Chemical Form	Half Life 1	Half Life 2	Half Life 3
Barium Carbonate	1. d	5. d	
Cyanide	0.4 d	2.5 d	33. d
Methanol	0.6 d	7. d	75. d
Glycine	0.26 d	2.5 d	53. d
Testosterone	1. d	6.25 d	
Estrone and estradiol	1. d		
Corticosterone	0.08 d	5. d	
Cortisol	0.15 d	0.92 d	
Inulin	0.07 d		
Delmopinol	0.08 d	0.5 d	
Dexloxiglumide	0.08 d	0.29 d	
Average	0.43 d	3.2 d	53.67 d

Other excretion information is available for total excretion, and, according to Leggett, may also be used for renal excretion data. The average half-time was 0.43 d (range 0.07-

1.0 d) for the fastest phase, 3.3 d (range, 0.29-7.0 d) for the intermediate phase, and 100 d (range 33-620 d). The fast phase typically represented 85% or more and the intermediate component about 5% of total urinary excretion.

3.3.2 Determining transfer and effective dose coefficients for generic model

Currently the most commonly used biokinetic modeling application is Dose and Risk Calculation Software (DCAL), which is available from the EPA or from the ORNL Center for Biokinetic and Dosimetric research websites [21]. DCAL is useful for determining the activity in organs over time for various radionuclides introduced into the human body via various forms of intake (ACTACAL module). It is also useful for determining the dose coefficients for the same cases considered by the ACTACAL module, using a combination of SEECAL (calculates the specific effective energies), EPACAL (calculates dose rates), and HTAB (tabulates the total effective dose coefficient and organ-specific dose coefficients). DCAL can be used by advanced users to implement user-created models for the calculation of the activity as a function of time, cumulative excretion, and effective dose coefficients.

The general procedure of implementing a model in DCAL is by modifying a .DEF file. An example of the .DEF file used for this generic carbon model to represent an average excretion rate/profile is presented in Appendix A. After creating or modifying a .DEF file, the DCAL module window is opened, and it is confirmed that the DCAL module is working in the same directory as the .DEF file location. To begin the ACTACAL module, the “Activity as $f(t)$ ” option must be selected by the user. A series

of questions are asked such as the nuclide name, the uptake pathway, and other options such as the age of the individual being exposed to the radiation. For the generic carbon model, it was always assumed that the individual was 7300 days old, or an adult. The child and younger cases could not be considered because of insufficient data. After the ACTACAL module has been run, a .ACT file will have been created in the working directory, containing the data for the activity as a function of time in all organs affected by the compound being considered. For cumulative excretion, the BIOTAB module can be implemented from the main module, but only the 24 hour urinary and fecal excretions are tabulated. For most case, this is sufficient, but for the case of this generic model development, more excretion information was needed, and it was calculated via integration, using the .ACT file as the data source.

Biokinetic models can be viewed mathematically as a system of first-order differential equations. This relatively complex system of differential equations is replaced with a relatively simple mathematically formulated estimation by the differential equation solver used in DCAL. It is assumed that the system may be estimated by linear differential equations over many time intervals or “time steps.” Specifically, each compartment is isolated and it is assumed that the rate of change in activity in the compartment can be described by the sum of a constant inflow rate of P and an outflow rate equal to the product of the current activity in the compartment, Y, and a transfer rate coefficient, R.

$$\frac{dY}{dT} = -RY + P \quad \text{[Equation 3.2]}$$

The solution for this differential equation is:

$$Y = \left(Y_0 - \frac{P}{R}\right)e^{-RT} + \frac{P}{R} \quad \text{[Equation 3.3]}$$

The integrated activity from time 0 to time T is:

$$Y_{INT} = \frac{1 - e^{-RT}}{R} \left(Y_0 - \frac{P}{R}\right) + \frac{PT}{R} \quad \text{[Equation 3.4]}$$

For recycling models such as the generic carbon model being proposed, these equations do not directly apply. Therefore, the solution for these compartments is determined by applying these equations iteratively until a solution with the desired accuracy is achieved.

In order to determine the transfer coefficients that would yield a urinary excretion profile similar to the available renal excretion data, a .DEF file was implemented using the previously defined transfer coefficients and best guesses for the unknown transfer coefficients. After the ACTACAL module was implemented on the .DEF file, the resulting .ACT file was manipulated to determine the cumulative urinary excretion over time, the cumulative fecal excretion, and cumulative breath excretion. The urinary excretion curve from the .ACT file was compared to a multiple scatter plot of the available excretion data. Adjustments were made to the unknown transfer coefficients in attempt to produce a more central average excretion curve. This process was repeated

many times, and due to its inefficient nature, other means of iterating on the unknown transfer coefficients to match the average urinary excretion curve were investigated.

The differential equation solver from Mathematica [105] was considered for solving the system of differential equations in a more efficient manner than DCAL [4]. Mathematica is a computational software program used in scientific, engineering, and mathematical fields. A system of differential equations can be solved quickly and easily using the NDSolve method from Mathematica. The means by which systems of differential equations are solved by NDSolve are not known because the module is proprietary. The step size is automatically adapted by NDSolve so that the estimated error in the solution is within predefined tolerances. Specifically, the precision is set to 9 decimal places.

In addition to NDSolve, another method contained in Mathematica that is useful for determining the unknown transfer coefficients in a more efficient process is the Manipulate command. An equation passed into the Manipulate method can be altered by varying any of the variables that the user would want to manipulate. For the case of solving this differential equation, the six unknown transfer coefficients were able to be manipulated while dynamically solving the system of differential equations using NDSolve. The commands that were used to solve a more simple set of differential equations for the case of injecting radiocarbon directly into the blood is presented in Appendix B. The resulting interface that is generated by the Manipulate command is presented in Figure 3.10.

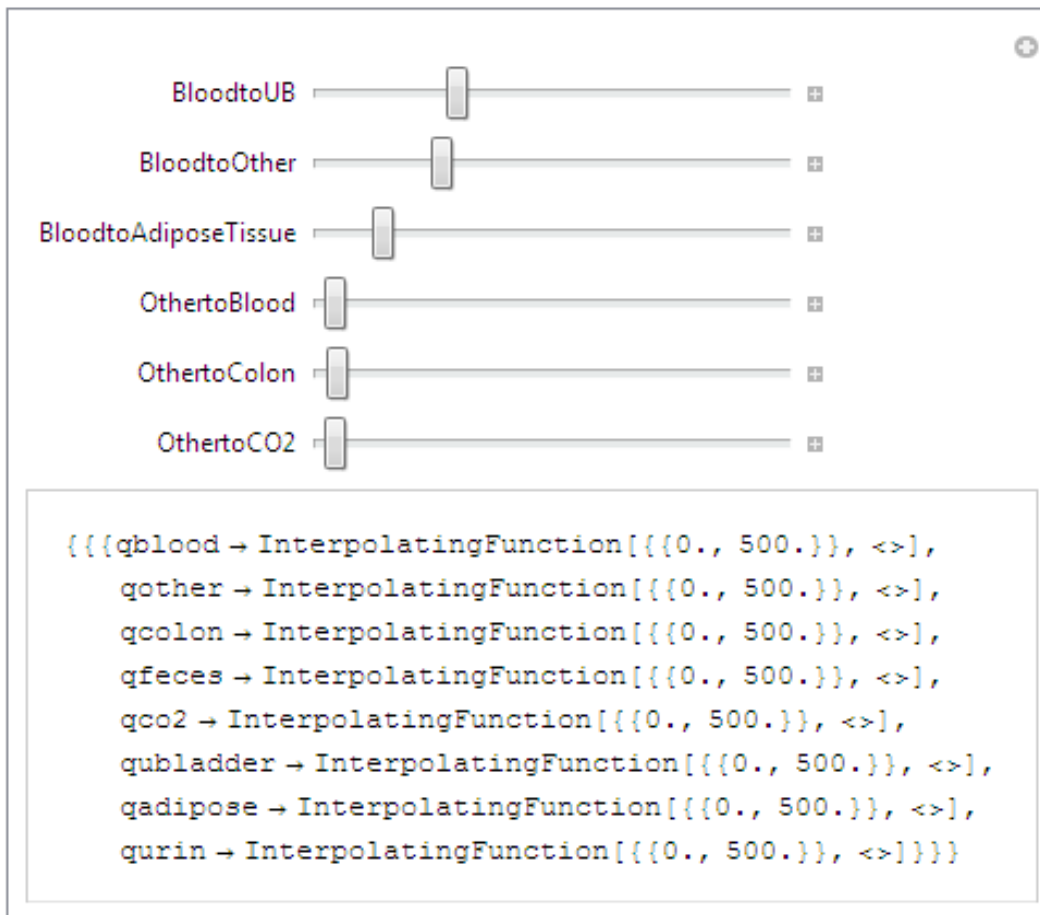


Figure 3.10 User interface generated by the Manipulate command in Mathematica

The ranges on each of the sliders were predefined in the original command from Appendix B. By sliding a specific slider from left to right, the transfer coefficient will increase. Sliding right to left will decrease the transfer coefficient. In order to determine the specific value of the transfer coefficient, the plus symbol on the right side of the slider can be activated to reveal a text box containing the current value of the transfer coefficient. The values of the transfer coefficients may also be manipulated using text input in the text box that is activated after clicking the plus symbol.

The Manipulate and NDSolve commands, alone, are not sufficient to aid in solving of the unknown transfer coefficients. In order to receive feedback on how an increase or decrease in the value of a transfer coefficient may affect the urinary excretion curve, the urinary excretion over a period of 100 days was dynamically plotted. Therefore, a chart was generated with two separate plots: a scatter plot of all the available excretion data normalized to the same total excretion and the urinary excretion curve produced by the model. Real-time, user-controlled curve fitting was able to be conducted so that the user could determine how the urinary excretion curve would change while altering the transfer coefficients. An example of how increasing the Blood to Urinary bladder transfer coefficient affects the urinary excretion curve is presented in Figure 3.11. In Figure 3.11, the scattered data is a plot of all the available excretion data being used as a benchmark and the solid line is the transforming urinary excretion curve produced by the model. When the transfer coefficient is increased in part B of Figure 3.11, the beginning portion of the curve increases dramatically due to an increase in the early transfer rate to the urinary bladder.

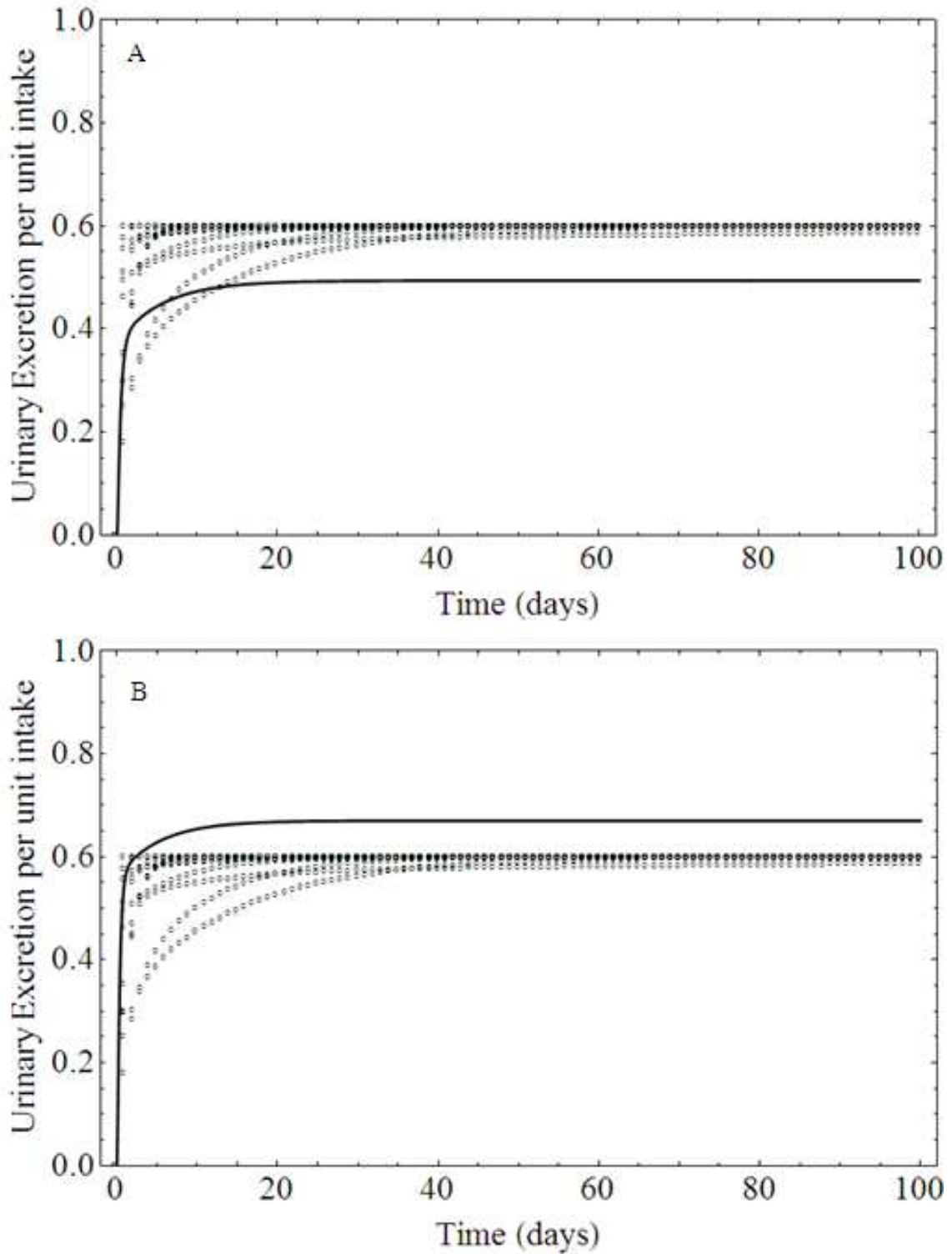


Figure 3.11 The effect of increasing the Blood to Urinary Bladder transfer coefficient.

Iteratively manipulating the transfer coefficients and viewing the effects of the manipulations, a reasonable urinary excretion fit was obtained. The corresponding urinary excretion curve is presented in Figure 3.12, where the dashed line is the benchmark excretion curve and the solid line is the model-generated urinary excretion curve. Note that the asymptotic excretion value is 0.6, which is the total urinary excretion fraction using the average generic case. In addition to fitting the urinary excretion curve, the proper excretion fractions were also fit simultaneously such that the excretion at 500 days post intake would be 60% renal, 25% fecal, and 15% exhaled.

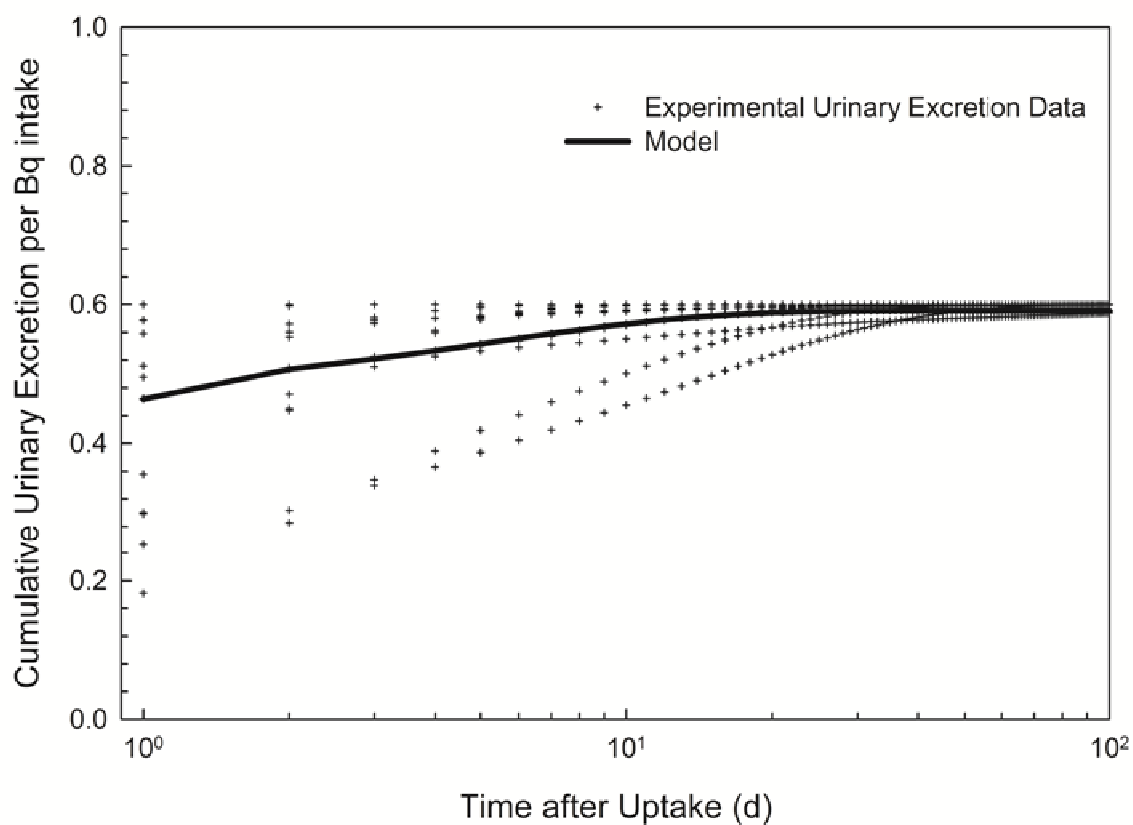


Figure 3.12 Urinary excretion curve output by the generic model average case.

After manipulating the transfer coefficients, it was apparent that each transfer coefficient affected different regions of the curve. The slope of the beginning of the curve (approximately 0 to 0.5 days for this case) was affected by the Blood to Urinary Bladder transfer coefficient; the slope of the next part of the curve from 0.5 to 2 days was altered using the Blood to Systemic (Short) transfer coefficient; the coefficient of the middle of the curve from 2 to approximately 20 days was affected by the Systemic (Short) to Blood transfer coefficient; and the final part of the curve was affected by the Systemic (Short) to Feces, Systemic (Short) to Breath, and Blood to Systemic (Long) transfer coefficients. The transfer coefficients used in the generic model for the average case are presented in Table 3.6. Many other transfer coefficients are used in the generic model to describe the transfer to and from other compartments. These may be referenced in Appendix A.

Table 3.6 Transfer coefficients used in the generic model

Compartment	Transfer coefficient (d ⁻¹)
Systemic (Short) to CO ₂ Model	0.062
Systemic (Short) to Blood	0.093
Systemic (Short) to Colon	0.037
Blood to Systemic (Short)	1.27
Blood to Bladder	1.51
Blood to Systemic (Long)	0.276

For the case of ingested radiocarbon, activity moves through the alimentary tract as described in the Human Alimentary Tract Model and is nearly completely (99%) absorbed to blood from the small intestine contents (SI). Blood loses activity with a half life of 5 hours, with 50% of the outflow assigned to the urinary bladder contents; 40% to

the short-term systemic compartment, and 10% to the long-term compartment. The short-term systemic tissue compartment loses activity with a half life of 3 days. Outflow from this compartment is divided as follows: 40% returns to Blood, 30% is secreted into the colon contents and subsequently excreted in feces, and 30% moves to blood compartment in the carbon dioxide model (Figure 8). Carbon entering the long-term retention compartment is assumed to be metabolized slowly to carbon dioxide, which moves to the blood compartment of the carbon dioxide model with a half-time of 100 d. A curve representing the total body retention as a fraction of initial uptake via injection is presented in Figure 3.13, comparing the updated model to the ICRP 71 GCM. The GCM retains more activity in the beginning, yet it drops of faster than the updated model after a period of approximately 500 days. This is due to the long term retention of the “Systemic Tissue (Long)” (or Adipose Tissue) compartment and the bone compartments from the CO₂ model. Not only is the ICRP model too conservative in its dose coefficient, it is also not conservative enough about the total body retention after a period of 500 days. Retention data for each organ in the updated model are presented in APPENDIX C.

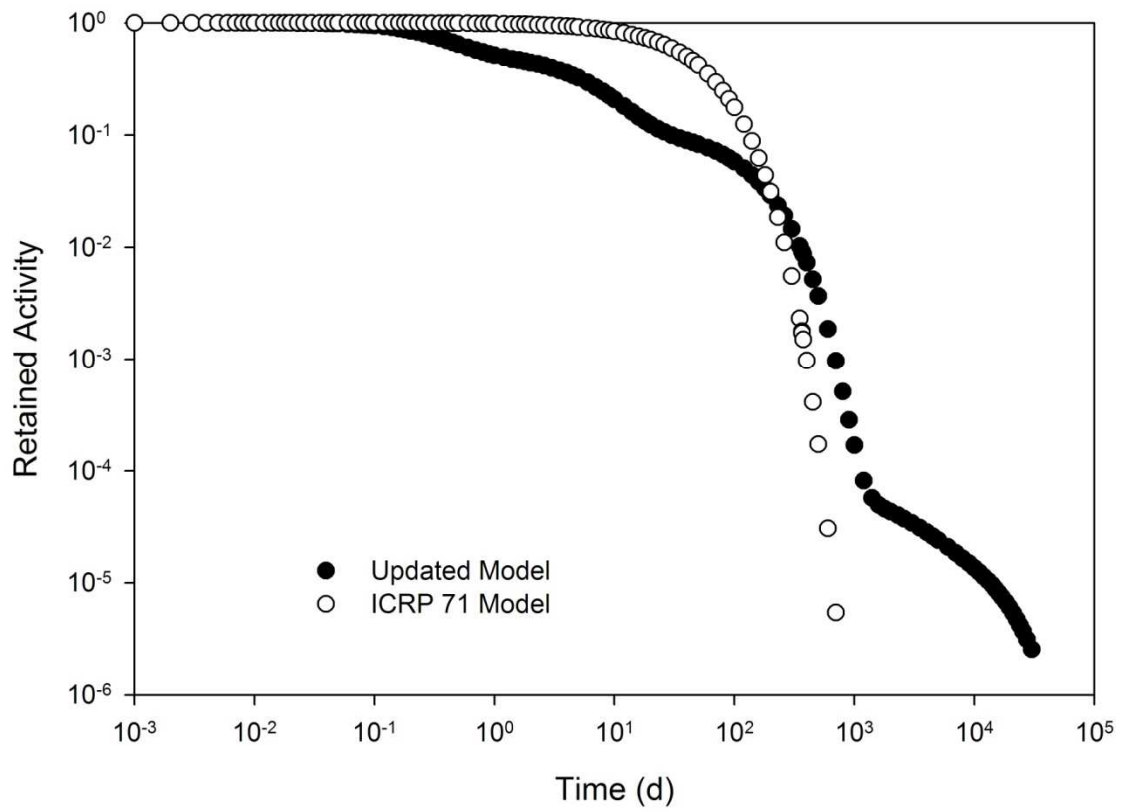


Figure 3.13 Total body retention following injection (updated vs. 40 d model)

The single compartment, 40 day half-life, model currently being used by the ICRP for generic radiocarbon does not resemble the multiple half life excretion rate that is observed for many compounds in literature. A comparison between the urinary excretion from the 40 day model and the excretion observed in experimental studies is displayed in Figure 3.14. Not only is the excretion not the same general shape as the other excretion curves, but it is also much lower. None of the excretion data represent a lower excretion than the generic carbon model at any time period. The reason is because the first, fast half life observed in all radiocarbon excretion is never greater than 1 day, while in the GCM, it is 40 days.

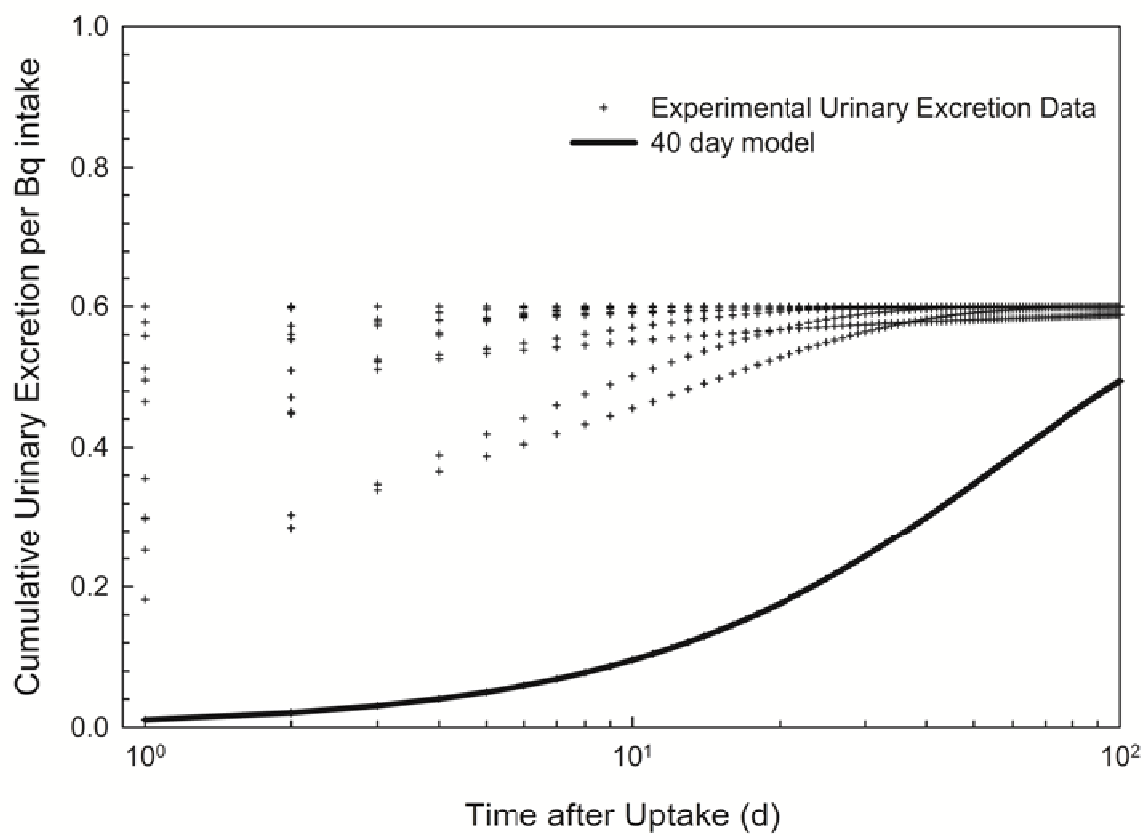


Figure 3.14 Cumulative excretion from the ICRP GCM model vs. observed excretion

After determining the transfer coefficients, a .DEF file was updated with the correct transfer coefficients so that DCAL could be used to calculate the effective dose coefficient. Using ACTACAL, SEECAL, EPACAL, and HTAB, the total effective dose coefficient was tabulated as 1×10^{-10} Sv Bq⁻¹ for the case of injection, when using the tissue weighting coefficients of ICRP 60 [50]. This dose coefficient is near the geometric mean, 1.21×10^{-10} Sv Bq⁻¹, of the dose coefficients for the radiocarbon compounds considered in Table 3.3 of this research. If more conservatism is wanted, and Systemic (Long) is modeled as “Other,” an effective dose coefficient of 2.4×10^{-10} Sv Bq⁻¹ is given. These effective dose coefficients are considerably lower than the previous generic radiocarbon model that yielded an effective dose coefficient of 5.80×10^{-10} Sv Bq⁻¹ [45].

Perhaps a less convoluted way of comparing the models is a comparison of the cumulative activity. The effective doses depend on tissue weighting coefficients, tissue specifications, and other arbitrary factors that convolute the comparison. DCAL can be used to determine the U_{50} values which are the number of nuclear transformations occurring in the body over 50 years. A few carbon compounds were chosen for comparison against the generic model and the ICRP 40 day model. The compounds were chosen because they represent both high and low effective dose coefficients. A comparison of U_{50} values are presented in

Table 3.7. The updated generic model is conservative in all cases besides xylose, which has a rather high effective dose coefficient. For other compounds with high effective dose coefficients such as glycocholic acid and triolein, the cumulative activity is comparable. The U_{50} data for each compartment of the updated generic model are presented in Table 3.8 for the case of injection. The compartment with the most nuclear transformations is the Systemic Tissues (Long) compartment followed by the Systemic Tissues (Short) compartment. The compartments with the least cumulative activity were the Cortical Bone Surface and Trabecular Bone Surface compartments.

Table 3.7 Relative U_{50} values for some carbon compounds

Model	Relative U_{50} (Nuclear transformation expressed as a multiple of the U_{50} value predicted by the updated generic carbon model)
Updated Generic Carbon Model	1
Benzene	0.03
Glycocholic Acid	0.58
Inulin	0.02
Triolein	0.86
Urea	0.61
Xylose	1.15
Generic Model in ICRP Publication 71	3

Table 3.8 U_{50} values for the compartments of the updated model

Region	U_{50} (total nuclear transformations per Bq of intake)
Blood	3.6E4
Systemic Tissue (Short)	2.5E5
Urinary Bladder Contents	4.5E3
Systemic Tissue (Long)	1.4E6
Colon Contents	1.4E4
Trabecular Bone Surface	3.4E3
Cortical Bone Surface	2.2E3
Trabecular Bone Volume	7.9E3
Cortical Bone Volume	2.4E4
Total Retained	1.8E6

This improved generic carbon model can be easily adapted to properly model numerous excretion patterns or rates. If more excretion data become available in future research, the model can be adapted to consider the updated excretion information. Also, if bioassay data is available, the model can be transformed to simulate the actual excretion profile for an individual to obtain a more accurate dose assessment. The generic

radiocarbon model suggested in this research is an improvement over the ICRP generic radiocarbon model because it is dynamic and more physiologically acceptable.

3.4 Recommendation for dosimetric treatment of radiocarbon

The manner in which the human body treats a radiocarbon substance is not dictated by the presence of radiocarbon, but rather the chemical form of the radiocarbon substance. Based upon this fact, the multiple ways in which the human body processes radiocarbon substances are as numerous as the number of radiocarbon substances in existence. Therefore, it is recommended that, if the radiocarbon substance is known, the specific biokinetic models and effective dose coefficients associated with that substance be used for dosimetric assessment. The established biokinetic models for specific radiocarbon compounds have been presented for eight substances in earlier sections of this document.

If the radiocarbon substance is not known, yet it is certain that an individual has taken up radiocarbon, it is suggested that the revised generic carbon model be used to for dosimetric assessment and setting dose limits. Currently, the ICRP suggests that in the latter case, a one-compartment whole body model be used with a 40 day half life. The updated generic model suggested in this paper is superior to the ICRP generic carbon model because it is more anatomically accurate, containing an alimentary tract, kidney bladder model, CO₂ model, an adipose compartment, and an “other” compartment for modeling systemic tissues. Also, the improved generic radiocarbon model is dynamic. It may be adapted to fit any excretion data that may become available in future research or

in a bioassay of someone exposed to radiocarbon. The updated generic model is able to match the urinary excretion data much better than the 40 day ICRP model because of its many components. The single exponential excretion of the ICRP 40 day model, although conservative, does not resemble the actual excretion data.

The final case that must be considered for radiocarbon uptake is dietary uptake. For this specific instance, it is suggested that the models proposed by Whillans or Richardson should be used. The model by Whillans is the superior model of the two because transfer coefficients were presented along with the model structure, while the model proposed by Richardson only presents the model structure. The transfer coefficients used in the Whillans dietary carbon model are based upon Reference man values and transfer coefficient suggested by Brown and Chant. The tissue weighting coefficients that are to be used in either of those models are not thoroughly explained, therefore the judgment of the user must be used to determine how to represent the tissues..

CHAPTER 4: CONCLUSIONS

When comparing the 5.8×10^{-10} Sv Bq⁻¹ effective dose coefficient produced by ICRP 71, 40-day-half-life, generic model to the effective dose coefficients of individual carbon compounds, it is apparent that the model greatly overestimates dose. The overestimate ranges up to a factor of 725 for carbon monoxide, and it is more than a factor of 9.2 greater than the median dose coefficient for the carbon compounds considered in Table 3.3 of this paper. The generic carbon model is also not representative of how the human body treats radiocarbon substances taken up by the human body. Most radiocarbon substances are expelled at a rate that is represented by multiple half lives, while the generic model is only a single half life.

The radiocarbon model proposed in this research improves in multiple areas over the current ICRP recommended model. The effective dose coefficients, 1×10^{-10} Sv Bq⁻¹ for modelling slow turnover as adipose and 2.4×10^{-10} Sv Bq⁻¹ for modelling slow turnover as “Other,” are near the geometric mean for the compounds listed in Table 3.3, 1.21×10^{-11} Sv Bq⁻¹. They are both within a factor of 3 for uncertainty of dose coefficients from biokinetic models that was discussed by Taylor. The model is more anatomically appropriate, including an alimentary tract, urinary bladder, and a model for metabolic production of CO₂. Perhaps the most attractive feature of the updated generic model is the adaptability. The only transfer coefficients that are fixed in the model are ones based upon pre-defined ICRP models. For instance, the GI tract transfer coefficients are based upon the ICRP 30 model, yet if the ICRP generates an updated GI tract model, the generic carbon model will be able to evolve and implement the updated GI tract

model. The six transfer rates that are not based upon predefined ICRP standards can be evaluated using excretion data. If more research on the excretion of radiocarbon compounds from the human body emerges, the model can be adapted to account for the new data. Also, the model can be adapted to match excretion data for unknown radiocarbon compounds from bioassay.

For the case of not knowing the chemical form of the radiocarbon taken up by an individual, the generic model is suggested; but if the radiocarbon compound taken up by an individual is known, the specific biokinetic models for that compound should be implemented. If the uptake of radiocarbon is from dietary sources, the model proposed by Whillans should be used for dosimetric assessment considering it is the most fully developed dietary carbon model available.

CHAPTER 5: FUTURE WORK

To develop a better radiocarbon biokinetic model, more excretion data are needed. The limiting condition in this research was the inability to conduct radiocarbon studies for any radiocarbon compound of interest. Therefore, the data used in this research were only available from previously studies on C¹⁴-labelled substances. Only urinary excretion data were available for many compounds, while breath and fecal excretion were only available for a few compounds and could not be used as a benchmark for creating the model. When more studies are performed on radiocarbon in the future, this model should be updated to reflect the newly available data.

Another potential improvement that can be made towards modeling radiocarbon is dietary carbon model development. The uptake of radiocarbon in food and drink is a significant concern, and the behavior of dietary carbon is different than the behavior of other forms of radiocarbon. Dietary carbon is expected to behave in the same manner as all nutrients entering the human body, being split into carbohydrates, fats, and protein prior to being fully metabolized. A comprehensive model of dietary radiocarbon should be created and tested against any dietary carbon data that is available for humans. The model created by Whillans was not thoroughly tested against experimental data, and no dietary radiocarbon model has been fully tested and explicitly defined (tissue weighting factors, transfer coefficients, etc.). There is a lack of dietary radiocarbon excretion data in the research, so future studies in dietary radiocarbon may require animal studies or epidemiological studies of populations that have ingested dietary radiocarbon (if they exist).

Ultimately, it would be ideal if each radiocarbon compound could be treated with a specific model for that compound, but determining the chemical form is not always a feasible, therefore a generic model will be required unless if the chemical form of the radiocarbon can be determined upon excretion. More research should be done on radiocarbon compounds that are not well known, but may be encountered in the workplace or environmental settings.

APPENDIX A: .DEF FILE USED IN DCAL FOR GENERIC RADIOCARBON

The .DEF file below uses Muscle for the Systemic Tissue (Long) compartment.

```

Generic model for carbon
  1 : Number of age groups
*****
*****
*****
7300 Adult
Blood      ->Other_5      1.2700E+00
Blood      ->UB_Cont     1.5100E+00
Blood      ->Muscle      2.7600E-01
Other_5    ->Blood       9.3000E-02
Other_5    ->Blood_1     6.2000E-02
Other_5    ->ULI_Cont    3.7000E-02
Muscle     ->Blood_1     6.9300E-03
Blood_1    ->Excreta     3.6500E+01
Blood_1    ->Other_1     6.0000E+01
Blood_1    ->Other_2     1.8000E+00
Blood_1    ->Other_3     3.0000E-01
Blood_1    ->Other_4     4.4000E-01
Blood_1    ->T_Bone-S    9.0000E-02
Blood_1    ->C_Bone-S    6.0000E-02
Blood_1    ->T_Bone-V    6.0000E-03
Blood_1    ->C_Bone-V    4.0000E-03
Blood_1    ->UB_Cont     6.5000E-01
Blood_1    ->ULI_Cont    1.5000E-01
Other_1    ->Blood_1     4.9910E+01
Other_2    ->Blood_1     1.3310E+00
Other_3    ->Blood_1     2.2180E-01
Other_4    ->Blood_1     1.6640E-02
Other_2    ->Blood_2     5.5450E-02
Other_3    ->Blood_2     9.2420E-03
Other_4    ->Blood_2     6.9310E-04
T_Bone-S   ->Blood_1     1.7330E-02
C_Bone-S   ->Blood_1     1.7330E-02
T_Bone-V   ->Blood_1     4.9320E-04
C_Bone-V   ->Blood_1     8.2190E-05
Blood_2    ->UB_Cont     1.0000E+03
EOF Data

```


Compartment Abbreviation	Compartment Description
St_Cont	Stomach Contents
SI_Cont	Small Intestines Contents
ULI_Cont	Upper Large Intestines Contents
Other_4	The main other compartment
Blood_2	CO ₂ model blood pool
Blood	Non-CO ₂ blood
UB_Cont	Urinary Bladder Contents
Excreta	Exhaled CO ₂
Other_1	1st Other compartment in CO ₂ model
Other_2	2nd Other compartment in CO ₂ model
Other_3	3rd Other compartment in CO ₂ model
T_Bone-S	Trabecular Bone Surface
C_Bone-S	Cortical Bone Surface
T_Bone-V_1	Trabecular Bone Volume 1
C_Bone-V_1	Cortical Bone Volume 1
T_Bone-V_2	Trabecular Bone Volume 2
C_Bone-V_2	Cortical Bone Volume 2

APPENDIX B: MATHEMATICA CODE

This section is composed of Mathematica code used to solve a system of differential equations for the simple case of injection in the revised generic radiocarbon model. The Manipulate and NDSolve commands are used in the first section to create a box with “sliders” used to manipulate specified variables and solve the system of differential equations respectively. Following the “slider” graphic, the Plot command dynamically plots the urine excretion while the sliders are used to change the value of a transfer coefficient. Also, three numbers are displayed dynamically: the total urine excretion, fecal excretion, and breath excretion.

```
Excreta =
  Join[Import["e1.csv"], Import["e2.csv"],
    Import["e3.csv"], Import["e4.csv"],
    Import["e5.csv"], Import["e6.csv"],
    Import["e7.csv"], Import["e8.csv"],
    Import["e9.csv"], Import["e10.csv"],
    Import["e11.csv"]];

Manipulate[{
  s = NDSolve[{
    qblood'[t] == -(BloodtoUB + BloodtoOther +
      BloodtoAdiposeTissue) * qblood[t] + OthertoBlood *
      qother[t],
    qother'[t] == BloodtoOther * qblood[t] - (OthertoBlood
      + OthertoColon + OthertoCO2) qother[t] ,
    qcolon'[t] == OthertoColon * qother[t] - 1 *
      qcolon[t],
    qfeces'[t] == 1 * qcolon[t],
    qco2'[t] == OthertoCO2 * qother[t] + 0.01 *
      qadipose[t],
```

```

qubladder'[t] == BloodtoUB * qblood[t] - 12 *
    qubladder[t],
qadipose'[t] == BloodtoAdiposeTissue * qblood[t] -
    0.01 * qadipose[t],
qurin'[t] == 12 * qubladder[t],
qblood[0] == 1,
qother[0] == 0,
qcolon[0] == 0,
qfeces[0] == 0,
qco2[0] == 0,
qubladder[0] == 0,
qadipose[0] == 0,
qurin[0] == 0
}, {qblood, qother, qcolon, qfeces, qco2, qubladder,
    qadipose, qurin}, {t, 500}]]
, {BloodtoUB, .05, 5}, {BloodtoOther, .01, 5},
{BloodtoAdiposeTissue, 0.01, 2}, {OthertoBlood, .01, 3},
{OthertoColon, .01, 2}, {OthertoCO2, .01, 2}]

```

The image shows a Mathematica interface with six sliders and a code block. The sliders are labeled as follows:

- BloodtoUB
- BloodtoOther
- BloodtoAdiposeTissue
- OthertoBlood
- OthertoColon
- OthertoCO2

Below the sliders, the following code is displayed:

```

{{qblood → InterpolatingFunction[{{0., 500.}}, <>],
 qother → InterpolatingFunction[{{0., 500.}}, <>],
 qcolon → InterpolatingFunction[{{0., 500.}}, <>],
 qfeces → InterpolatingFunction[{{0., 500.}}, <>],
 qco2 → InterpolatingFunction[{{0., 500.}}, <>],
 qubladder → InterpolatingFunction[{{0., 500.}}, <>],
 qadipose → InterpolatingFunction[{{0., 500.}}, <>],
 qurin → InterpolatingFunction[{{0., 500.}}, <>]}}}

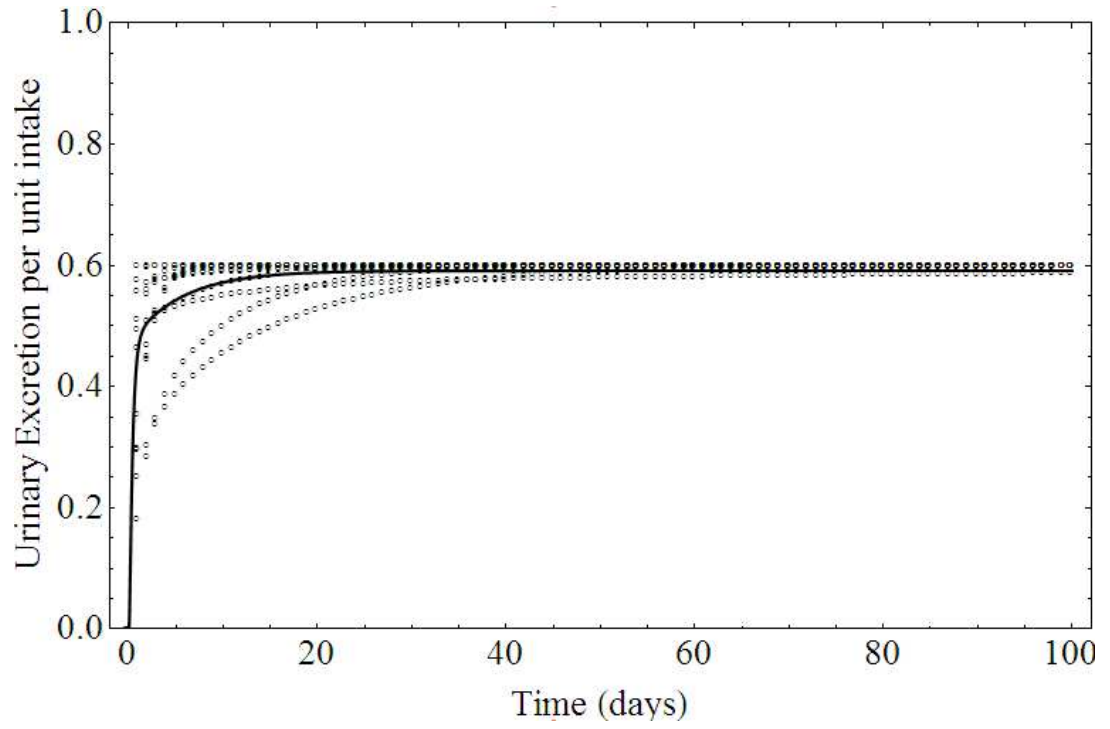
```

```

Dynamic[
  {Show[Plot[{Evaluate[qurin[t] /. s]}, {t, 0, 100},
    PlotStyle -> {Black, {Thick, Black}},
    PlotRange -> {0, 1},
    Frame -> True,
    FrameLabel -> {"Time (days)", "Urinary Excretion per
      unit intake"},
    LabelStyle -> {Large}],
    ListPlot[Excreta, PlotStyle -> {Thin, Black},
      PlotMarkers -> {\[EmptySmallCircle]}]
  ],

```

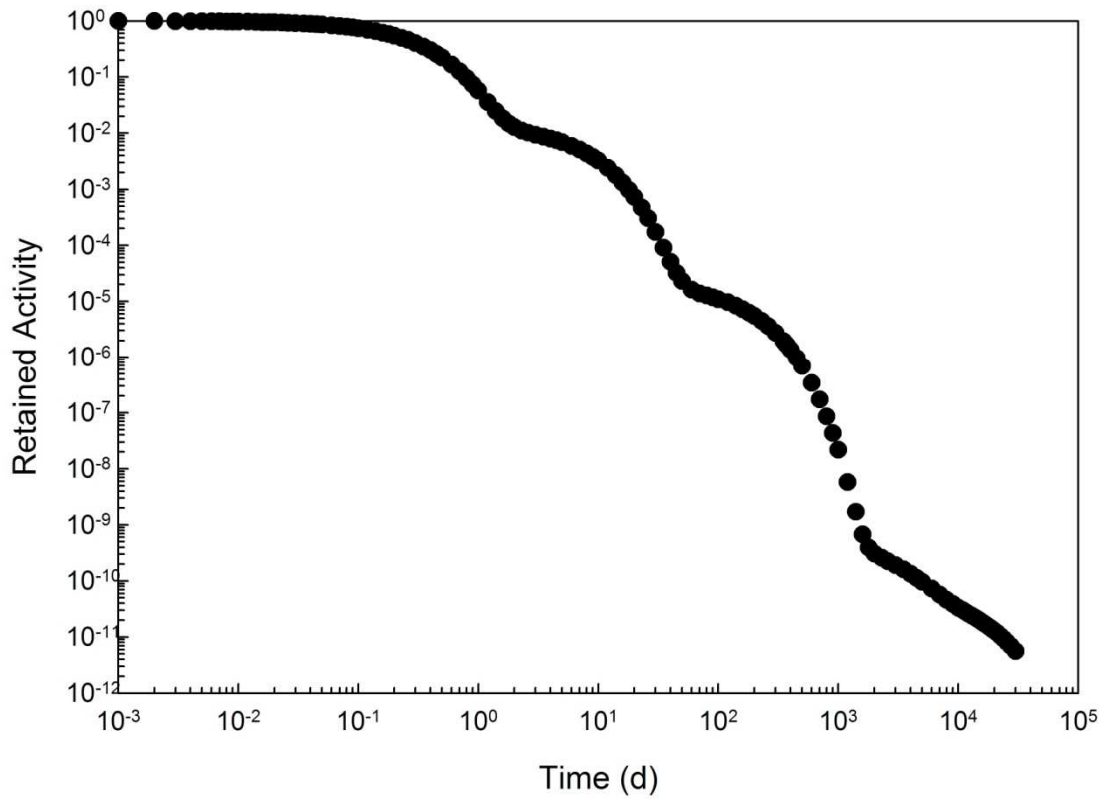
```
Evaluate[{qurin[500] /. s, qfeces[500] /. s, qco2[500]
/. s}]]]
```



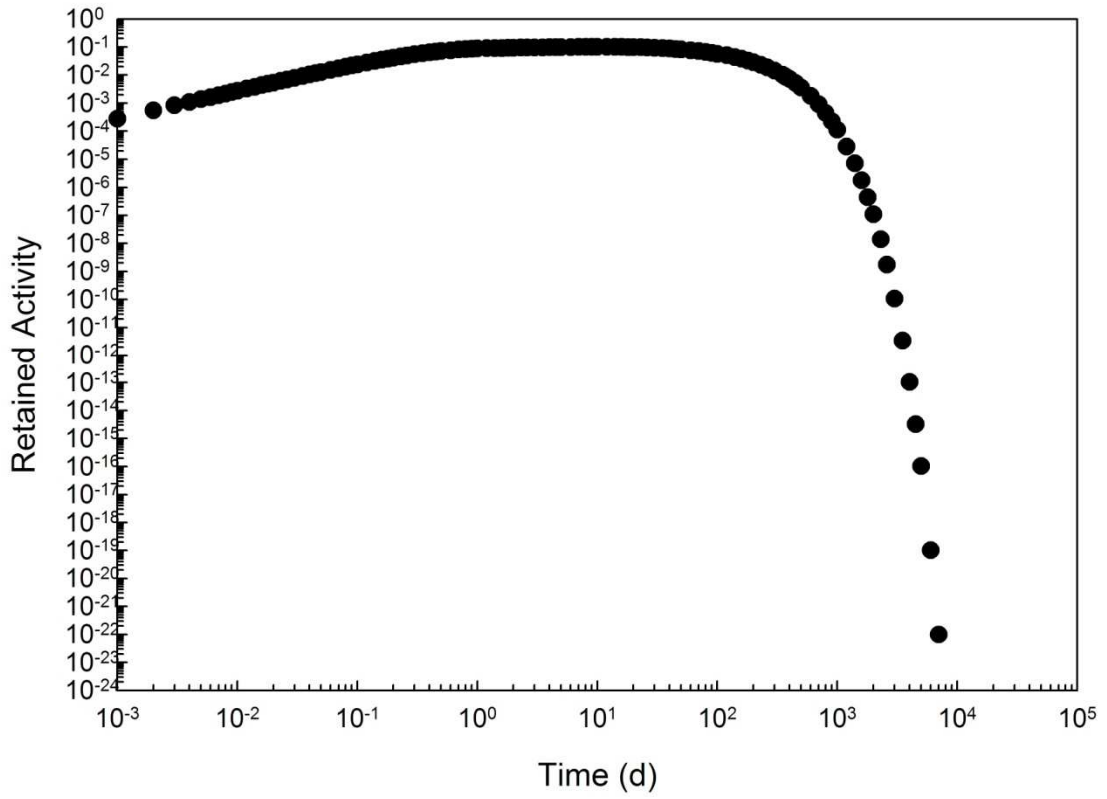
```
, {{0.599689}, {0.15083}, {0.248666}}}
```

APPENDIX C: RETAINED ACTIVITY IN EACH COMPARTMENT OVER TIME

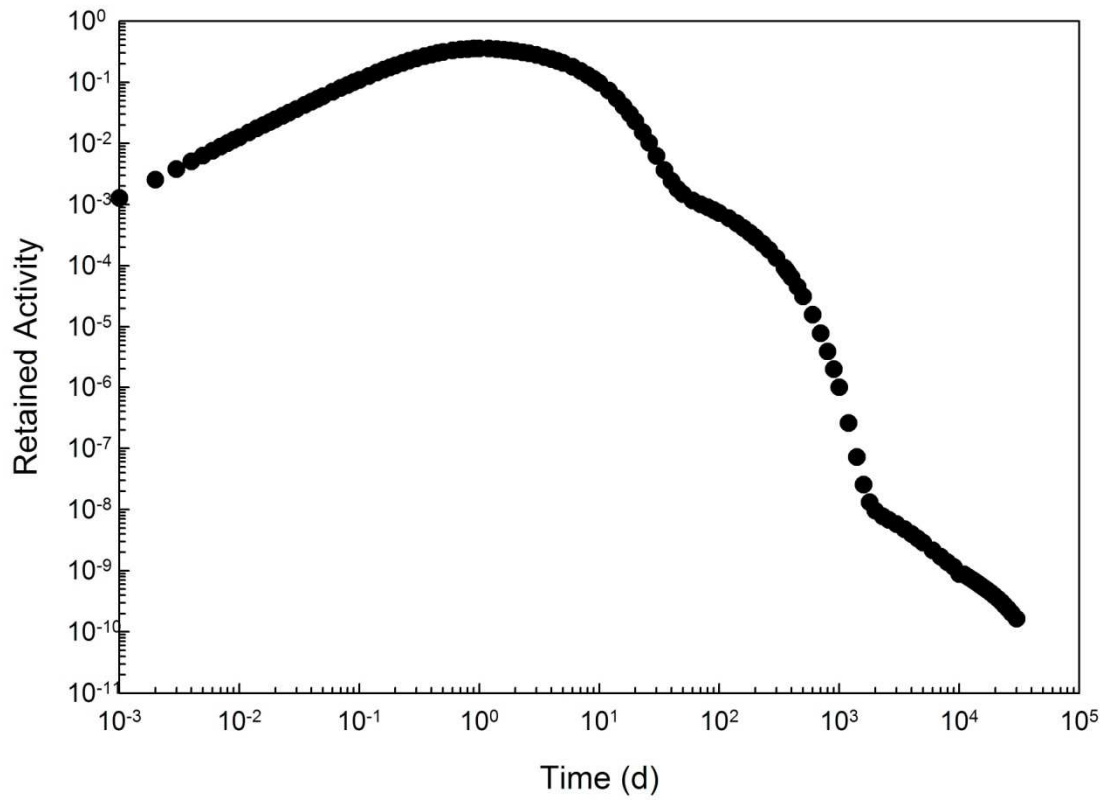
BLOOD



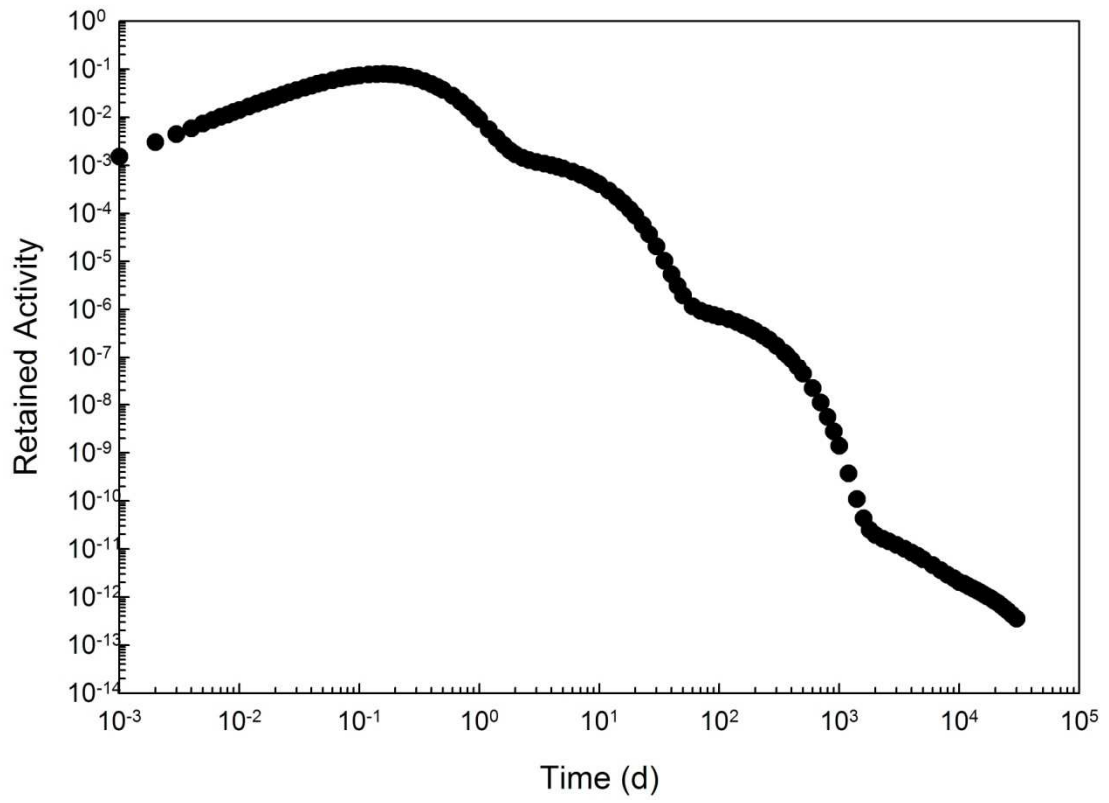
SYSTEMIC TISSUE (LONG)



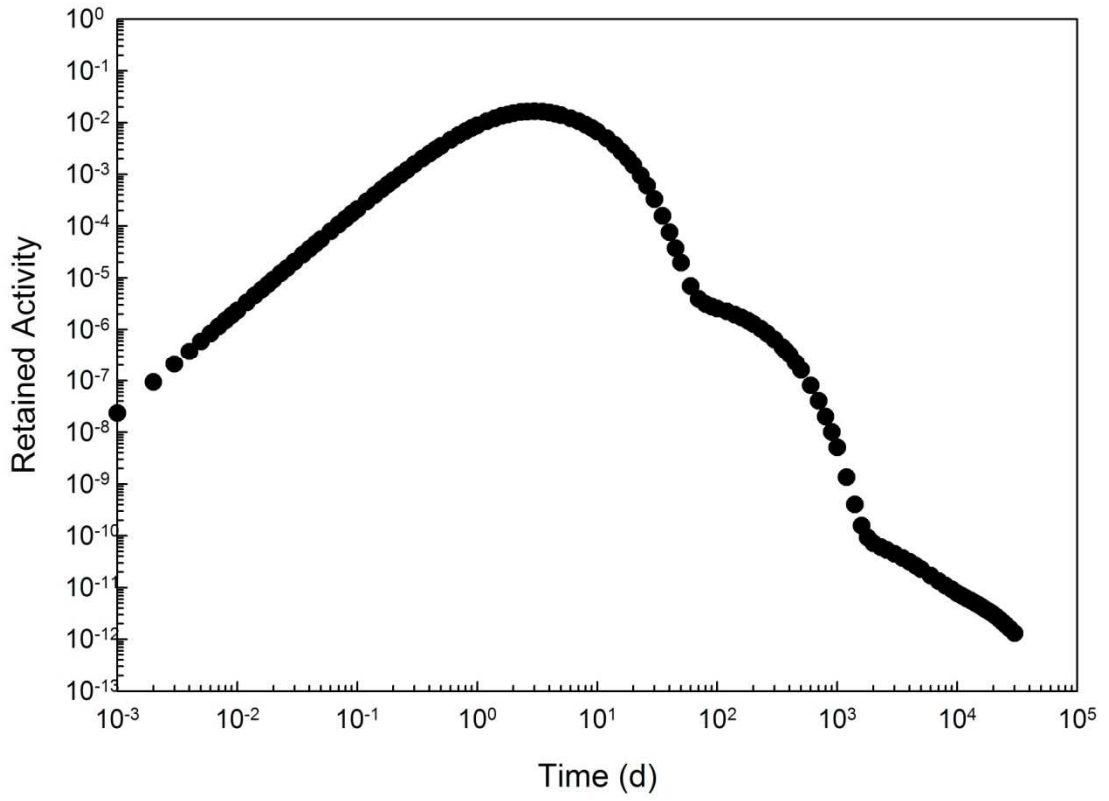
SYSTEMIC TISSUE (SHORT)



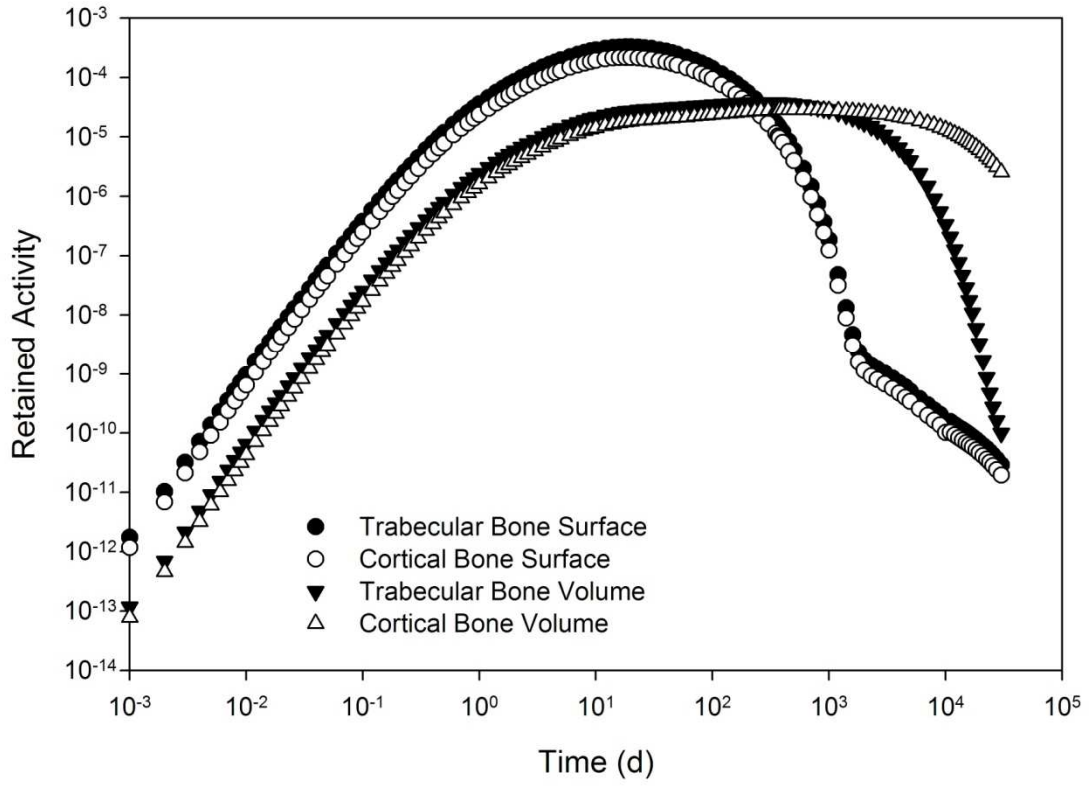
URINARY BLADDER



COLON



BONE



APPENDIX D. RADIATION PROTECTION DOSIMETRY

JOURNAL ARTICLE SUBMISSION

A GENERIC BIOKINETIC MODEL FOR CARBON-14

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The generic biokinetic model currently recommended by the ICRP for the treatment of systemic radiocarbon assumes uniform distribution of activity in tissues and a biological half-time of 40 d. This model is intended to generate cautiously high estimates of dose per unit intake of C-14 and, in fact, generally predicts a much higher effective dose than systemic models that have been developed on the basis of biokinetic studies of specific carbon compounds. The simplistic model formulation precludes its application as a bioassay model or adjustment to fit case-specific bioassay data. This paper proposes a new generic biokinetic model for systemic radiocarbon that is less conservative than the current ICRP model but maintains sufficient conservatism to overestimate the effective dose coefficients generated by most radiocarbon-compound-specific models. The proposed model includes two systemic pools with different biological half-times representing an initial systemic form of absorbed radiocarbon, a submodel describing the behaviour of labelled carbon dioxide produced in vivo, and three excretion pathways: breath, urine, and faeces. Generic excretion rates along each path are based on multi-phase excretion curves observed in experimental studies of radiocarbon. The generic model structure is designed so that the user may adjust the level of dosimetric conservatism to fit the information at hand and may adjust parameter values for consistency with subject-specific or site-specific bioassay data.

INTRODUCTION

Many biokinetic models exist for specific carbon-14-containing compounds, yet due to the large amount of radiocarbon substances, more forms of radiocarbon have not been modelled. The biokinetics of systemic radiocarbon is dependent on the carbon compound taken into the body and the location of the radioactive atom within the molecule⁽¹⁾. Internally deposited ¹⁴C-labelled compounds have residence time ranging from a few hours⁽²⁾ to several months⁽³⁾. The distribution of radiocarbon in the body and the pathway of excretion are also dependant on the chemical properties of the carbon compound taken

into the body. In a study by Taylor⁽¹⁾, it was determined that the effective dose coefficients for different internally deposited, ¹⁴C-labelled compounds vary over at least three orders of magnitude.

The International Commission on Radiological Protection (ICRP) provides compound-specific models for radiocarbon compounds such as carbon monoxide, carbon dioxide, methane, and inulin. For other radiocarbon compounds that do not have a specific model, the ICRP recommends a dosimetrically cautious model. This generic model was first recommended in ICRP Publication 30⁽⁴⁾ for the treatment of ¹⁴C-labelled compounds that have been inhaled or ingested. The recommended use of the generic model is for either the uptake of an unknown radiocarbon compound or the uptake of a form of radiocarbon without a predefined biokinetic model. The generic model is based upon the average rate of carbon intake for Reference Man⁽⁵⁾ and the total mass of carbon in the body of Reference Man⁽⁵⁾. Using 16 kg for the total body mass of carbon in and 0.3 kg d⁻¹ for the average daily carbon intake, a half life of approximately 40 days is calculated. In ICRP Publication 68⁽⁶⁾ and 71⁽⁷⁾, it was assumed that carbon is instantaneously and uniformly distributed in the body tissue and excreted with a half time of 40 days. An effective dose coefficient of 5.8×10^{-10} Sv Bq⁻¹ for inhaled or ingested C-14 was calculated by the ICRP using this model and assuming rapid and virtually complete absorption to blood.

The effective dose coefficients for most carbon compounds that have been researched appear to be greatly overestimated by the ICRP generic radiocarbon model based on comparison with dose coefficients generated by available carbon-compound-specific models⁽¹⁾. The purpose of this paper is to propose a new generic systemic biokinetic model for carbon-14 that may be used for the assessment of internal exposure to radiocarbon compounds in the workplace. The intended use of this model is for situations where either the form of the internally deposited ¹⁴C is unknown or the biokinetics of that form of carbon has not been established.

An effort has been made to include the major paths of movement and the major pathways of excretion for most carbon compounds deposited in the body so that the model can be adjusted on the basis of case-specific data to improve dose estimates for specific cases. For instance, adjustments may be made to the model to alter the rate at which the carbon is excreted from the body or the pathways of radiocarbon excretion.

The proposed model is less conservative than the ICRP Publication 71 generic model for carbon, but it also accounts for the possible long term retention of radiocarbon in the body. Compared to the effective dose coefficients of some of the specific forms of radiocarbon that have been studied, the proposed model is still more likely to overestimate than underestimate dose per unit intake of ¹⁴C in the workplace. If it is suspected that the model may underestimate the tissue doses or effective dose, the transfer coefficients may be modified to yield a longer retention time than the baseline values provided in this paper.

In this paper, some of the current radiocarbon models are presented along with their experimental excretion data and model characteristics. An updated generic model is then proposed and compared to some of the current radiocarbon models. In addition, examples are given to show how the transfer coefficients may be modified for improved dose estimates when case-specific information is available.

CURRENT RADIOCARBON MODELS

Many radiocarbon biokinetic models have been developed for specific radiocarbon compounds. The manner in which radiocarbon compounds are processed by the human body is dictated by the chemical form of the radiocarbon. Excretion data and common anatomical characteristics were the primary source of information used in the development of the generic radiocarbon model proposed here.

Excretion Data

Excretion data are available for many of the carbon compounds that have been studied. Specifically, the urinary excretion data are available for most compounds in literature, while the breath excretion, faecal excretion, and plasma concentration data are less frequently specified.

The urinary excretion of the radiocarbon compounds that were considered in this research are described by a three – or less – component exponential. The excretion for the ICRP generic carbon model is described by a single, 40 day, exponential elimination. More compartments are required to model the fast, moderate, and slow components of elimination that are not being considered by the single compartment elimination of the ICRP 71 model.

The excretion characteristics vary among all chemical forms of radiocarbon. For compounds with available excretion data, the cumulative urinary excretion ranges from a factor of 0.01 to 1 of the total radiocarbon taken up; the cumulative faecal excretion ranges from a factor of 0 to 0.99 of the total radiocarbon taken up; and the cumulative breath excretion ranges from 0 to 0.95 of the total radiocarbon taken up. On average, the excretion profile was approximately 60% urinary, 25% exhaled, and 15% faecal. The compounds upon which these data are based are: K[1-¹⁴C]-cyanide⁽⁸⁾, [1-¹⁴C]-methanol⁽⁹⁾, [¹⁴C(U)]-glucose^(10, 11), [2-¹⁴C]-glycine^(12, 13), [4-¹⁴C]-cholesterol⁽³⁾, [4-¹⁴C]-testosterone^(14, 15), [16-¹⁴C]-estrone – [16-¹⁴C]-estradiol-17β⁽¹⁶⁾, [4-¹⁴C]-corticosterone⁽¹⁷⁾, [4-¹⁴C]-cortisol⁽¹⁸⁾, [2-¹⁴C]-thymidine⁽¹⁹⁾, [¹⁴C]-inulin^(2, 20), [2-acetate-¹⁴C]-diethylenetriaminepenta acetate (DTPA)⁽²¹⁾, [¹⁴C]-nitrobenzene⁽²²⁾, [¹⁴C]delmopinol⁽²³⁾, and [¹⁴C]dexloxiglumide⁽²⁴⁾. Of those compounds, cyanide and methanol were studied in rats, and the other listed compounds were studied in human subjects.

The typical elimination rates also varied from compounds such as inulin with a single component half life of 1.67 h to compounds such as methanol with 85% leaving at a half life of 0.6 days, 10% leaving at a half life of 7 days, and 5% leaving at a half life of 75 days. The reported urinary excretion rates consisted of up to three components: a fast component, intermediate component, and slow component. The average biological half-time of the fast phase was approximately 0.4 days (range 0.07 – 1.0 d), the intermediate phase was approximately 3 days (range 0.29 – 7 d), and the slow phase was approximately 70 days (range 33 – 620 d).

Characteristics of published models for inhaled forms of carbon

Biokinetic models have been implemented for many radiocarbon compounds. Due to the assortment of chemical forms of radiocarbon, the model structures vary among all compounds, but the models share a few common characteristics.

Glycocholic acid, xylose, triolein, and urea were studied by Gunnarsson, Leide-Svegborn, et al.⁽²⁶⁻³⁶⁾ Each of these models shares the common feature of having an integrated CO₂ model. Models such as the biokinetic model describing methane⁽²⁰⁾, the

model proposed by Whillans for dietary carbon⁽²⁵⁾, the model for glycine-2-¹⁴C^(12, 13), and others also feature an integrated CO₂ model. CO₂ is an important compound in the human body due to its critical role in cellular respiration and pH regulation within the human body.

Another common feature in many carbon models is the long term retention of radiocarbon in the adipose tissue. To represent the long term component of elimination and the tendency of radiocarbon to slowly metabolize with adipose tissue, a portion of the internalized radiocarbon is deposited in an adipose tissue compartment that represents long term retention in several of the previous biokinetic models. A few examples of models that considered long term retention of radiocarbon in adipose tissue are models for glycocholic acid⁽³⁴⁾, xylose⁽³⁴⁾, triolein⁽³⁵⁾, methanol (based on a rat study)⁽⁹⁾, and cyanide (based on a rat study)⁽⁹⁾.

Other systemic compartments and their half-times vary among the available radiocarbon biokinetic models. In certain models, the liver is an important component, while other models do not consider the liver. The same is true for the kidneys, gall bladder, and other tissues. For the generic case, an "Other" compartment may be used to represent this category of tissues. The details of how this may be accomplished are included in the description of the generic model.

Characteristics of dietary carbon models

In a model proposed by Richardson and Dunford^(32, 83), dietary carbon entering the body is divided into carbohydrates, lipids, and proteins. Simple and complex versions of the biokinetic model are proposed. The complex version divides carbohydrates into glucose and glycogen, lipids into fatty acids and adipose fat, and protein into amino acids and soft tissue proteins. The model is intended for use with hydrogen (³H), carbon (¹⁴C), nitrogen (¹⁵N), and oxygen (¹⁸O) radionuclides. Transfer coefficients and effective dose coefficients were not presented by Richardson and Dunford for ¹⁴C substances.

A model proposed by Whillans⁽²⁵⁾ also separates all dietary carbon into carbohydrates, fats, and proteins. A central CO₂/bicarbonate compartment is supplied by these three components. The CO₂ compartment also exchanges activity with some bone compartments. All three excretion pathways (urinary, fecal, and breath) are present. The model was also presented with radiocarbon-specific transfer coefficients. The transfer coefficients were based upon intakes by Reference Man⁽⁵⁾ and suggestions by Brown and Chant⁽³⁴⁾.

A third model proposed for the intake of dietary carbon was developed by Galeriu et al⁽²⁸⁾. This model uses anatomical compartments and transfer coefficients determined from reference physiological constants such as metabolic rates, body energy densities, and empty body masses. The transfer coefficients were developed for various farm animals, but using the same method, transfer coefficients could be developed for human beings.

DESCRIPTION OF THE PROPOSED GENERIC MODEL

The generic ¹⁴C model proposed in this paper is based upon common (but not universal) characteristics of current biokinetic models and excretion data derived from biokinetic studies on human subjects or rats. The model accounts for the short, moderate, and long half times that are present in many of the radiocarbon compounds that have been studied.

The pathways of intake considered are inhalation, excretion, and injection/wound. The pathways of excretion considered are renal, faecal, and exhaled. The structure of the model is presented in Figure 1. Upon ingestion, the radiocarbon proceeds according to the Human Alimentary Tract Model (HATM)⁽³⁶⁾. Radiocarbon reaching the contents of the small intestines is nearly completely absorbed to blood (99%). In the baseline case the blood pool has a half life of approximately 5 hours. C-14 reaching the blood is transferred to the urinary bladder contents (50%), a systemic tissue compartment to be processed at a moderate rate ($T_{1/2} = 3$ days) (40%), and another systemic tissue compartment to be processed at a slower rate ($T_{1/2} = 70$ days) (10%). The systemic tissue compartment with a faster metabolic rate represents systemic tissues other than adipose tissue, while the slower metabolic compartment represents long term retention in adipose tissue.

Approximately 40% of the activity entering the moderate systemic tissue compartment is transferred back to the blood, 30% is metabolized to carbon dioxide, and the final 30% is secreted into the contents of the colon to be excreted as faeces. The longer lived systemic tissue compartment slowly metabolizes the radiocarbon to carbon dioxide. The radiocarbon entering the carbon dioxide compartment is treated according to a simplified version of the CO₂/bicarbonate model proposed by Leggett⁽³⁷⁾. The CO₂/bicarbonate model was modified to simplify implementation of the model by reducing the total number of compartments and pathways, to make the model more consistent with the scheme of the updated generic model, and to improve predictions of the long-term urinary excretion rate by including additional phases of transfer from soft tissues to the urinary excretion pathway¹. Transfer coefficients for the modified CO₂ model (Figure 2) are presented in Table 1⁽³⁸⁾. Activity entering the CO₂ model is deposited in the Blood 1 compartment.

Inhaled radiocarbon is treated according to the Human Respiratory Tract Model (HRTM)⁽³⁹⁾ to be absorbed in the blood and swallowed to the alimentary tract. The activity entering the blood is treated in the same manner as the radiocarbon that reaches the blood via the small intestines contents, while the activity entering the alimentary tract is treated according to the HATM.

Transfer coefficients for the systemic portion of the model were determined by using the NDSolve and Manipulate commands in Mathematica, Version 7.0⁽⁴⁰⁾, which allows for dynamic numeric differential equation solving. The urine excretion data were available for many radiocarbon compounds. The renal excretion over time was plotted for each compound by normalizing the maximum cumulative urinary excretion. Meanwhile, a curve representing the urinary excretion of the model in Figure 1 was displayed on the same graphic so that the change in the shape of the urinary excretion curve could be viewed as the transfer coefficients were adjusted using Manipulate and NDSolve. The transfer coefficients were fine-tuned until the urinary excretion curve represented a central fit of all the urinary excretion rate data (Figure 3). The ideal fit was represented by a blood half time of 5 hours, and two systemic half times of 3 days and 70 days, which is on the same order as the available urinary excretion data for radiocarbon compounds. In addition, the average excretion profile (60% in urine, 25% in breath, and 15% in faeces) was used as a benchmark for the fine-tuning of the transfer coefficients. The final transfer coefficients that were calculated using the described methods are presented in Table 2.

¹ Personal communication from R. Leggett, Oak Ridge National Laboratory, Oak Ridge, TN 37830.

The model is dynamic because the systemic transfer coefficients may be adjusted to compensate for specific cases. For instance, if the urinary excretion were higher, the fraction being transferred to the systemic tissues could be decreased accordingly. The half times of either or both systemic tissue compartments could be increased if more conservatism is wanted. The transfer coefficients presented in Table 2 represent a slightly conservative estimate of the average radiocarbon compound.

COMPARISON WITH OTHER MODELS

The effective dose coefficient calculated for this model varies according to how the system compartments are treated. If the moderate systemic compartment is modelled as “Other,” and the slow systemic compartment is modelled as “Adipose Tissue,” the dose coefficient is approximately 1×10^{-10} Sv Bq⁻¹ when using ICRP 60⁽⁴¹⁾ tissue weighting factors for the case of injection. If both compartments are modelled as “Other,” the dose coefficient is approximately 2.4×10^{-10} Sv Bq⁻¹ when using ICRP 60 tissue weighting factors for the case of injection. This is a factor of about 2.5 to 6 less than the dose coefficient calculated using the ICRP generic radiocarbon model. All dose coefficient calculations were computed using Dose and Risk Calculation Software (DCAL), Version 9.0⁽⁴²⁾.

A less convoluted relationship is a comparison of the cumulative activity in the body over time. Using DCAL, the U_{50} values – number of nuclear transformations at 50 years – were calculated for some low and high effective dose coefficient compounds and are presented in Table 3. It can be observed when comparing the U_{50} data with other compounds that the generic carbon model is of the same order or greater than the other models. Therefore the proposed generic ¹⁴C model, although less conservative, is still conservative when compared to most radiocarbon compounds on a cumulative activity basis.

A comparison of the urinary excretion from the modified generic radiocarbon model and the ICRP 71 generic carbon model is presented in Figure 4. The excretion of the 40 day model was normalized to 60% urinary excretion for comparison with the modified generic model and urinary excretion from previous radiocarbon studies. The excretion of the 40 day model greatly lags the observed excretion and the updated model excretion over the first 100 days. The whole body retention of the updated model and the 40 day model are displayed in Figure 5. Up until approximately 500 days, the 40 day model lags the model presented in this paper. After 500 days, the 40 day model retains less than predicted by the updated model because of the longer half lives of the bone compartments in the CO₂ model and the adipose tissue/systemic tissue (long) compartment.

MODIFICATION FOR SPECIFIC CASES

In practice, the radiocarbon model presented in this paper may be manipulated on a case-by-case basis. One instance in which manipulation of the model may be necessary is for the case of a radiocarbon compound that is known to be excreted at a different rate or with a different excreta allocation than the generic case. Another example in which the model may be changed is for an unknown radiocarbon compound that is not being excreted at the same rate or with the same excreta distribution predicted by the generic carbon model. An additional instance that may require manipulation of parameter values

is if inadequate information about the radiocarbon compound has been collected and more conservatism is wanted.

An example of a radiocarbon compound with an excretion rate that is greater than the generic case is DTPA. Intravenously injected DTPA is excreted from the body quickly, with half-times of approximately 1.4 minutes (~60%), 14.3 minutes (~20%), and 95 minutes (~20%)⁽²¹⁾. These half times are much shorter than the half-times associated with the transfer coefficients in Table 2. In addition, nearly all of the DTPA is excreted in the urine as opposed to the 60% assumed in the average case. Adjusting the half-times of the systemic compartments in Figure 1 and iteratively solving the differential equations using Manipulate and NDSolve in Mathematica, a new set of transfer coefficients may be determined for DTPA. The Blood to Urinary Bladder transfer coefficient is increased to approximately 70 d^{-1} , which is associated with a half-time of approximately 14 minutes. The Systemic Short to Blood transfer coefficient is increased to 10 d^{-1} , the Blood to Systemic Short transfer coefficient is decreased to 0.7 d^{-1} , and the Blood to Systemic Long transfer coefficient is decreased to 0.1 d^{-1} . By altering the half-times of these components, the three-component excretion of DTPA is able to be modelled.

For the case of an unknown radiocarbon substance that has been internally deposited, the average case (Table 2) may be used, but if the observed bioassay data are not similar to what is predicted by the average case, the half-times can be altered to match the unknown compound. For instance, if the excretion rate of an unknown radiocarbon substance is approximately the same as the average case, but the pathway of excretion is different, the model may be altered to fit that case. If the excretion is 20% in urine, 20% in breath, and 60% in faeces, a new set of transfer coefficients can be determined to match this differing excretion pattern. For this case, Blood to Urinary Bladder is decreased to 0.35 d^{-1} and Systemic Short to Colon is increased to 0.95 d^{-1} . Altering these two half times changes the excretion profile to 60% in faeces, 20% in breath, and 20% in urine.

The final instance where manipulation of the average case may be necessary is when more conservatism is wanted. For this case, the half times of the systemic compartments can be increased, which will yield much lower transfer coefficient, a higher number of nuclear transformations in the body, and a higher effective dose coefficient. The magnitude of the increased conservatism is determined by how much longer the half-times are adjusted.

Alterations to the generic model are complex due to the recycling portion of the model. As a result, a simple formula cannot be applied to easily manipulate the excretion rate or excretion pathways. The differential equations must be solved to determine the excretion curve and the excretion fractions. In this paper, Mathematica was used, but other resources are also available to iteratively solve the systems of differential equations so that the proper alterations may be prepared.

SUMMARY

The generic radiocarbon model that has been proposed is different than the ICRP generic carbon model for a few distinct reasons. The model is less conservative than the 40 day half-life model, but still maintains enough conservatism to have an effective dose coefficient greater than the majority of radiocarbon compounds with known effective dose coefficients. Also, the model contains a respiratory tract, alimentary tract, and two

systemic compartments as opposed to the single 40 day half-life compartment. By having more compartments, the time rate of excreta resembles the multi-phase excretion curves observed in experimental studies of radiocarbon. The model is dynamic having the ability to emulate a specific retention profile. It may also be adjusted to be more or less conservative. The model presented in this paper is reasonably consistent with the experimental data available on radiocarbon and models human excretion data more precisely than the ICRP 40 day half life model. For dietary carbon, the models developed by Whillans⁽²⁵⁾ and Richardson and Dunford^(32, 83) are promising for the internal dosimetry of radiocarbon taken up in the human diet.

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Table 1. Transfer coefficients for the modified CO₂ model used in conjunction with the updated generic radiocarbon model.^a

Path	Transfer Coefficient (d ⁻¹)
Blood 1 to Excreta (exhalation)	36.2
Blood 1 to Excreta (via skin)	0.3
Blood 1 to Urinary bladder contents	0.65
Blood 1 to Colon contents	0.15
Blood 1 to Soft tissue 0	60
Blood 1 to Soft tissue 1	1.8
Blood 1 to Soft tissue 2	0.3
Blood 1 to Soft tissue 3	0.44
Blood 1 to Trabecular bone surface	0.09
Blood 1 to Cortical bone surface	0.06
Blood 1 to Trabecular bone volume	0.006
Blood 1 to Cortical bone volume	0.004
Soft tissue 0 to Blood 1	49.91
Soft tissue 1 to Blood 1	1.331
Soft tissue 2 to Blood 1	0.2218
Soft tissue 3 to Blood 1	0.01664
Soft tissue 1 to Blood 2	0.05545
Soft tissue 2 to Blood 2	0.009242
Soft tissue 3 to Blood 2	0.0006931
Blood 2 to Urinary bladder contents	1000
Trabecular bone surface to Blood 1	0.01733
Cortical bone surface to Blood 1	0.01733
Trabecular bone volume to Blood 1	0.0004932
Cortical bone volume to Blood 1	0.00008219

^aPersonal communication from R. Leggett, Oak Ridge National Laboratory, Oak Ridge, TN 37830

Table 2. Baseline transfer coefficients for the systemic compartments of the generic radiocarbon model.

Path	Transfer Coefficient (d ⁻¹)
Systemic (Short) to CO ₂ Model	0.062
Systemic (Short) to Blood	0.095
Systemic (Short) to Colon	0.070
Systemic (Long) to CO ₂ Model	0.0099
Blood to Systemic (Short)	1.27
Blood to Bladder	1.51
Blood to Systemic (Long)	0.276

Table 3. Comparison of cumulative activity in the body for carbon-14 labelled substances.

Path	Nuclear transformations (multiple of the new generic model U_{50})
Updated Generic Model	1
Benzene	0.03
Glycocholic Acid	0.58
Inulin	0.02
Triolein	0.86
Urea	0.61
Xylose	1.15
ICRP 71 GCM	3

Figure 1. Model structure of the proposed generic radiocarbon biokinetic model.

Figure 2. Model structure of the modified CO₂/bicarbonate biokinetic model.

Figure 3. Urinary excretion rates, based upon exponential fits, for many radiocarbon compounds. The central line in a fit to the experimental data.

Figure 4. Urinary excretion curves for the ICRP 71 40 day model, the modified generic carbon model presented in this paper, and previously studied radiocarbon compounds.

Figure 5. Total body retention of the ICRP 71 model and the modified generic carbon model presented in this paper.

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