REVISED VERSION
01 December 2016

BASIS FOR THE ICRP'S UPDATED BIOKINETIC MODEL FOR CARBON INHALED AS CO_2

Rich Leggett

Environmental Sciences Division
Building 1509, Room 205
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37831

Email: rwl@ornl.gov
Phone: 865-576-2079

The work described in this manuscript was sponsored by the Office of Radiation and Indoor Air, U. S. Environmental Protection Agency (EPA), under Interagency Agreement DOE No. 1824-S581-A1, under contract No. DE-AC05-00OR22725 with UT-Battelle.

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ABSTRACT

The International Commission on Radiological Protection (ICRP) is updating its biokinetic and dosimetric models for occupational intake of radionuclides in a series of reports called the OIR (Occupational Intake of Radionuclides) series. This paper describes the basis for the ICRP's updated biokinetic model for inhalation of radiocarbon as carbon dioxide (CO_2) gas. The updated model is based on biokinetic data for carbon isotopes inhaled as carbon dioxide or injected or ingested as bicarbonate (HCO_3^-). The data from these studies are expected to apply equally to internally deposited (or internally produced) carbon dioxide and bicarbonate based on comparison of excretion rates for the two administered forms and the fact that carbon dioxide and bicarbonate are largely carried in a common form (CO_2-HCO_3^-) in blood. Compared with dose estimates based on current ICRP biokinetic models for inhaled carbon dioxide or ingested carbon, the updated model will result in a somewhat higher dose estimate for ^{14}C inhaled as CO_2 and a much lower dose estimate for ^{14}C ingested as bicarbonate.

INTRODUCTION

Carbon-14 ($T_{1/2}$ = 5730 y) is produced in nuclear reactors through neutron activation of ^{13}C, ^{14}N, and ^{17}O present in the fuel, cladding, coolant, moderator, and structural material (Davis 1977, Koarashi et al. 2005; NAS 2012). Especially high levels of ^{14}C are produced in pressurized heavy water reactors (PHWRs) from neutron activation of large quantities of ^{17}O present in the heavy water used as a reactor coolant and moderator (Kim et al. 2009). A substantial portion of ^{14}C released from PHWRs and certain other types of reactors, as well as ^{14}C discharged from fuel and cladding at fuel reprocessing plants, is in the form of carbon dioxide ($^{14}CO_2$) (Koarashi et al. 2005; Magnusson 2007, Kim et al. 2009; EPRI 2010).

Because ^{14}C is a pure weak beta emitter, its presence in the body can be assessed only through measurement of ^{14}C in excreta and interpretation of findings using biokinetic models. Measurement of urinary ^{14}C is most commonly used for monitoring exposure of workers to $^{14}CO_2$, even though exhalation is by far the dominant route of ^{14}C excretion (CNSC 2006).

The biokinetic model for occupational intake of airborne CO_2 used by the International Commission on Radiological Protection (ICRP) since the 1980s assumes complete, instantaneous absorption from the lungs to blood and uniform distribution of activity throughout the body (ICRP 1981, 1994). Total body retention, R(t), of carbon is described by the sum of three exponential terms:

$$R(t) = 0.18e^{-0.693t/0.00347} + 0.81e^{-0.693t/0.0417} + 0.01e^{-0.693t/40}, \qquad \text{(Eq. 1)}$$

where t is in days. The first two terms were derived as a fit to measurements of exhaled ^{14}C in healthy human subjects following intravenous administration of ^{14}C-labeled bicarbonate (Winchell et al. 1970), considering that carbon dioxide and bicarbonate are largely carried in a common chemical form in blood. The third term represents a small component of extended retention indicated by studies of the fate of carbon isotopes inhaled as CO_2 in laboratory animals. The model was not intended as a bioassay model and does not address specific excretion pathways, although the early and intermediate phases of loss indicated in Eq. 1 can be assumed to represent exhaled activity.

The ICRP is updating its biokinetic and dosimetric models for intake of radionuclides by workers in a series of reports called the OIR (Occupational Intake of Radionuclides) series. An updated biokinetic model that serves as a bioassay model as well as dosimetry model for inhaled carbon dioxide gas is introduced in OIR Part 2 (in press). This paper describes the basis for that model and compares its predictions with those of the long-standing ICRP model for ^{14}C inhaled as carbon dioxide (Eq. 1).

METHODS

The biokinetic model for inhaled CO_2 described here is a revision of an earlier model for radiocarbon ingested as bicarbonate or inhaled carbon dioxide (Leggett 2004). The structure of the earlier model (called the '2004 model' in the following) is shown in Figure 1.

The 2004 model was developed for the primary purpose of improving dose estimates for ^{14}C-bicarbonate ingested in drinking water compared with the highly conservative estimates based on the ICRP's generic biokinetic model for carbon used since the early 1980s (ICRP 1981, 1989, 1993; Smith and Thorne 2015). The 2004 model was based largely on biokinetic data for radiocarbon-labeled bicarbonate and, to a lesser extent, carbon dioxide, and the assumption of virtually identical biokinetics of carbon following its ingestion or intravenous injection as bicarbonate or inhalation as carbon dioxide. That assumption is based on comparative biokinetic data for carbon inhaled as carbon dioxide or ingested or intravenously injected as bicarbonate, and the fact that carbon dioxide and bicarbonate are largely carried in a common form (CO_2-HCO_3^-) in blood (Skipper 1952; Winchell et al. 1970; Meineke et al. 1993). The assumption of identical biokinetics of carbon entering the body as bicarbonate or carbon dioxide was also made in the development of the model described in this paper. Broadly similar systemic kinetics of the carbon label has been observed for other forms of carbon including ^{13}C-glucose (Masuda et al., 2016), but attention was restricted here to bicarbonate as a reasonably well established biokinetic analogue of inhaled carbon dioxide.

The present model incorporates the following primary changes from the 2004 model:

Reduction of the number of tissue compartments. The model described in this paper contains 8 tissue compartments compared with 14 tissue compartments in the 2004 model. Two soft-tissue compartment were used in the 2004 model to depict an early, rapid (minutes) exchange of carbon

between blood and tissues that is of physiological interest but unimportant for purposes of radiation protection. A relatively complex model of carbon kinetics in bone in the 2004 model arose in part from the assumption that each intermediate phase (half-time) of removal of carbon from the body reflected loss with that half-time from bone surface was well as soft tissue. The revised model eliminates the assumed parallel losses from bone surface and soft tissues. The bone compartments used in the present model are standard compartments in ICRP biokinetic models for workers and members of the public: trabecular bone surface, cortical bone surface, trabecular bone volume, cortical bone volume.

As in the 2004 model, no attempt has been made in the revised model to depict the behaviour of carbon in terms of explicitly identified organs (other than bone) or specific physiological processes. Rather, body tissues are divided into bone and total soft tissues, and each of these main model components is divided into compartments representing different phases of carbon retention indicated by reported studies. For simplicity, exhalation of carbon via the lungs and loss through the skin are depicted as a direct transfer from blood to the environment, and loss in urine is depicted as direct transfer from blood to the urinary bladder content.

Addition of a blood compartment. In the 2004 model, blood is depicted as a single, well-mixed pool. This implies that the rate of removal of activity to the urinary bladder contents is at all times parallel to the rate of removal to the environment in expired air, but this does not appear to be the case during the first day after intake (Whillans and Johnson 1984). A second blood compartment was added to depict a relatively slow phase of removal of carbon in urine that results in non-parallel losses of carbon in breath and urine. This second blood compartment essentially represents transfer of urea carbon from tissues to the urinary bladder contents.

Longer residence time on bone surface. The residence time of carbon on bone surface following intake of CO_2 or bicarbonate is inferred from the early rate of decline of bone carbon observed in rodent studies. Association of the early bone kinetics of carbon with specific portions of bone involves considerable uncertainty, as does extrapolation of carbon kinetics from rodents to humans. For these reasons the modeled residence time of carbon on bone surface has been increased over that assumed in the 2004 model.

Parameter values of the revised model are based on the following data sources: (1) biokinetic data for ^{14}C in healthy human subjects over a 3-week period following inhalation of $^{14}CO_2$ (Whillans and Johnson 1984); (2) observed kinetics of ^{13}C or ^{14}C in human subjects following administration of labeled bicarbonate (Winchell et al. 1970; Irving et al. 1983; Hoerr et al. 1989; Barstow et al. 1990; Elia et al. 1992, 1995; Meineke et al. 1993; Leese et al 1994; Saccomani et al. 1995); (3) the time-dependent distribution and excretion of the carbon label in laboratory animals following administration of carbon dioxide or bicarbonate (Bloom et al. 1946; Buchanan 1951a, 1951b; Skipper 1952; Brues and Stroud 1952; Brues and Buchanan 1952; Buchanan and Nakao 1955; Joftes 1967; Shipley and Gibbons 1975; Sahlu et al. 1988; Ram et al. 1999).

Movement of carbon in the body is depicted as a system of first-order processes and described in terms of transfer coefficients (fractional flow per day), sometimes called transfer rates. The transfer coefficients generally are secondary values derived from primary parameter values in the form of deposition fractions or removal half-times. The reader is referred to Leggett 1997 (p.

592) for definitions of these terms, a description of the method of derivation of the primary parameter values, and illustrations of the derivation of transfer coefficients from the primary parameter values.

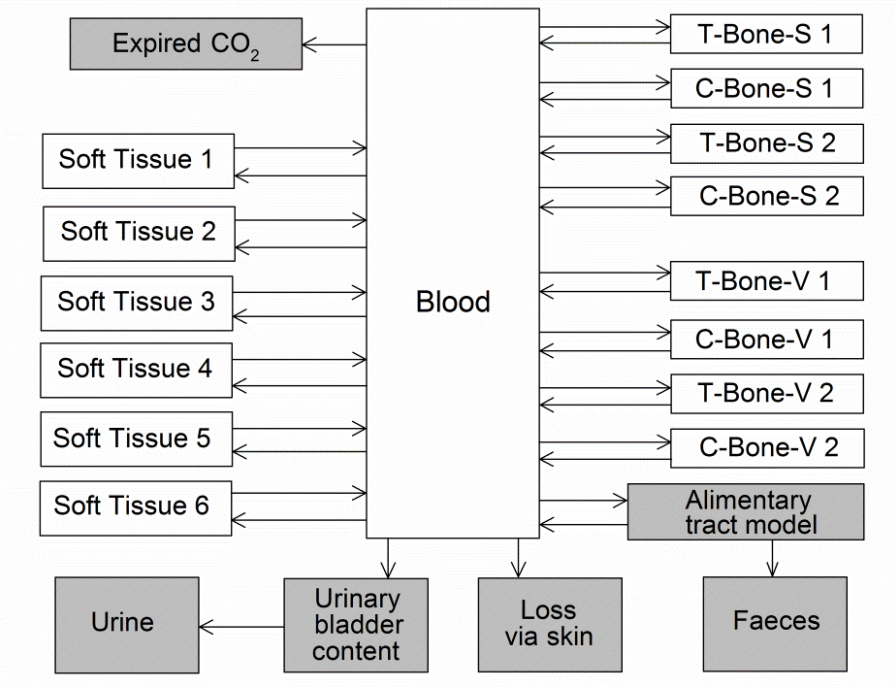

Figure 1. Structure of earlier biokinetic model for carbon entering blood as carbon dioxide or bicarbonate (Leggett 2004).

Results of the controlled study of inhaled $^{14}CO_2$ in human subjects (item 1 above) were considered in development of the 2004 model only in a qualitative sense, i.e., insofar as they indicated different phases of removal of ^{14}C from the body and shapes of the ^{14}C exhalation and urinary excretion curves at 1 d to 3 wk after intake. This data set plays a more important role in the present model in that model predictions of time-dependent exhalation and urinary excretion of ^{14}C are required to be quantitatively as well as qualitatively consistent with excretion data from the study of Whillans and Johnson (1984). Achieving quantitative agreement with the data of Whillans and Johnson required estimation of typical values for daily urinary excretion and daily exhalation of stable carbon by an adult male, because the data were reported as specific activity of ^{14}C, i.e., activity per unit mass of stable carbon in urine or breath. A reference value of 5 g for daily urinary excretion of stable carbon was taken from ICRP Publication 23 (1975). A reference value of 230 g for daily exhalation of carbon was based on theoretical considerations. It is an estimated typical value based on consideration of various presumably realistic daily nutrient intakes by an adult male and resulting production and exhalation of CO_2.

In addition to findings of Whillans and Johnson (1984) for inhaled $^{14}CO_2$, results of nutrient oxidation studies involving administration of labeled bicarbonate to human subjects were considered in the determination of different phases of loss of activity from the body over the

early hours or days post exposure to labeled bicarbonate. As illustrated in Figure 2, results of such studies generally are reported as transfer coefficients of simple compartmental models, derived from measurements of the carbon label in expired air and sometimes other excreta.

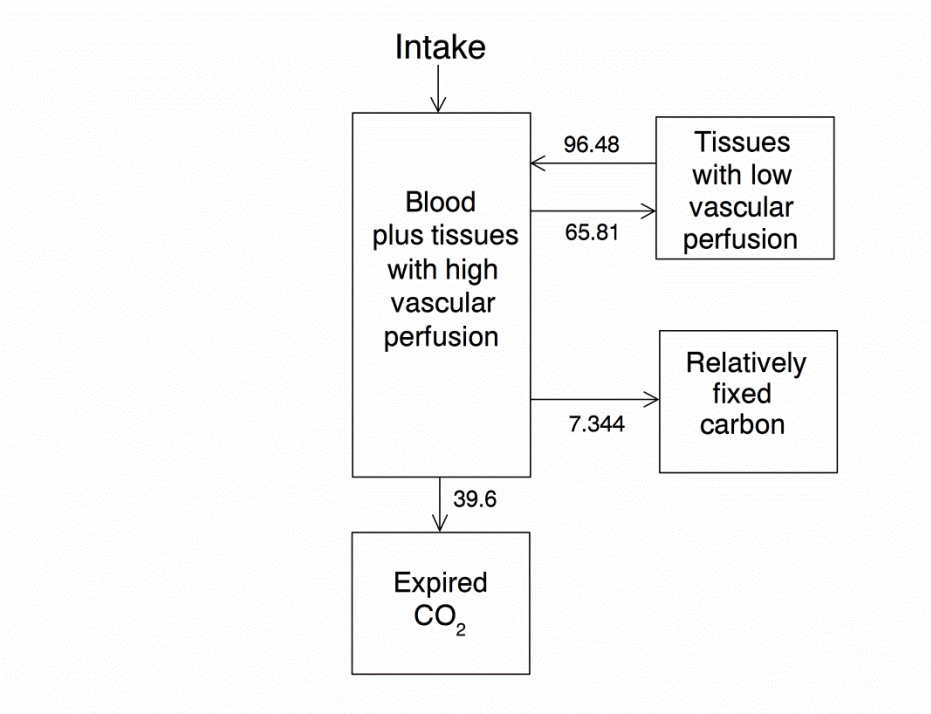

Figure 2. Biokinetic model of Winchell et al. (1970) for ^{14}C administered intravenously as ^{14}C-bicarbonate. The numbers are transfer rates (d^{-1}) derived as means of 13 sets of transfer rates determined by fitting the model to measured ^{14}C exhalation rates in each of 13 subjects.

Transfer coefficients of the updated ICRP model describing phases of loss over periods of months or years were based on data for laboratory animals administered labeled carbon dioxide or bicarbonate. Short- and long-term phases of retention in bone were assumed to represent retention of carbon in bone surface and volume, respectively. Extrapolation of data from laboratory animals to humans involved consideration of species differences in metabolic rates and bone turnover rates. Most of the animal studies have involved rats and mice, which are expected to lose the carbon label considerably faster than human at all times after exposure, including late losses due to bone turnover.

Based on findings for human subjects administered labeled bicarbonate (and generally supported by animal data), model parameters were set so that total losses via expired air, urinary excretion, faecal excretion, and through skin account for 96.8%, 2%, 0.4%, and 0.8%, respectively, of total loss of carbon atoms that initially reach blood as carbon dioxide or bicarbonate.

RESULTS

The structure of the updated biokinetic model for carbon taken into the body as carbon dioxide or bicarbonate is shown in Figure 3. Transfer coefficients are listed in Table 1.

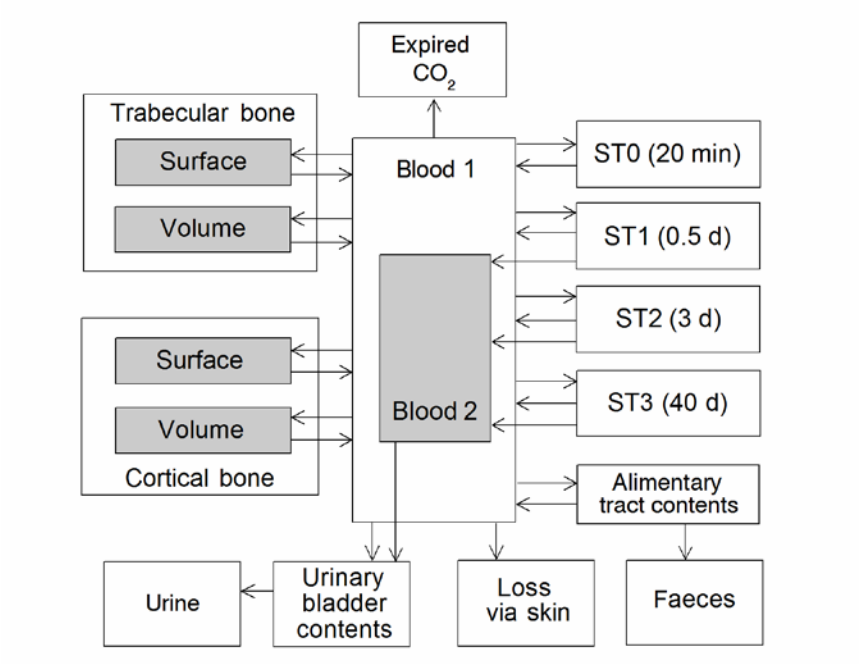

Figure 3. Structure of the updated model. The times in the boxes representing soft tissue (ST0, ST1, ST2, ST3) are biological half-times.

Absorbed carbon is assigned to a blood pool called Blood 1. Activity leaves Blood 1 at 100 d^{-1} ($T_{1/2}$ = 10 min), with 60% of the outflow going to a soft tissue compartment called ST0 with a biological half-time of 20 min; 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 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 reference rate of bone turnover (ICRP 2002), which differs for trabecular and cortical bone.

Table 1. Transfer coefficients for the model for inhaled carbon dioxide[a]

From	To	Transfer coefficient (d^{-1})
Blood 1	Excreta	36.5[b]
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	0.000493
Cortical bone volume	Blood 1	0.0000821

[a]Applicable also to intake of bicarbonate
[b]36.2 d^{-1} in expired air and 0.3 d^{-1} via skin.

As illustrated in Figure 4, model predictions are reasonably consistent with observed rates of exhalation and urinary excretion of ^{14}C over 1-20 d following inhalation of $^{14}CO_2$ (Whillans and Johnson 1984). The observations are from a controlled study involving $^{14}CO_2$ inhalation by six male volunteers and are expressed as specific activity, i.e., Bq g^{-1} C (stable carbon) in expired air or urine. Model predictions in Bq d^{-1} were converted to specific activities assuming daily losses for an adult male of 5 g of stable carbon in urine (ICRP 1975) and 230 g in expired air (a central estimate based on various theoretical calculations of the body's daily production of CO_2). Figure 4 is similar in appearance to Figure 7 of Leggett (2004), which compared predictions of the 2004 model with the same data of Whillans and Johnson (1984). However, the model predictions shown in Figure 7 of Leggett (2004) were normalized (separately for urine and breath) to measured values at 18 d and provided only a comparison of observations with the qualitative patterns of exhalation and urinary excretion of ^{14}C predicted by the 2004 model, from 1-18 d after inhalation of CO_2.

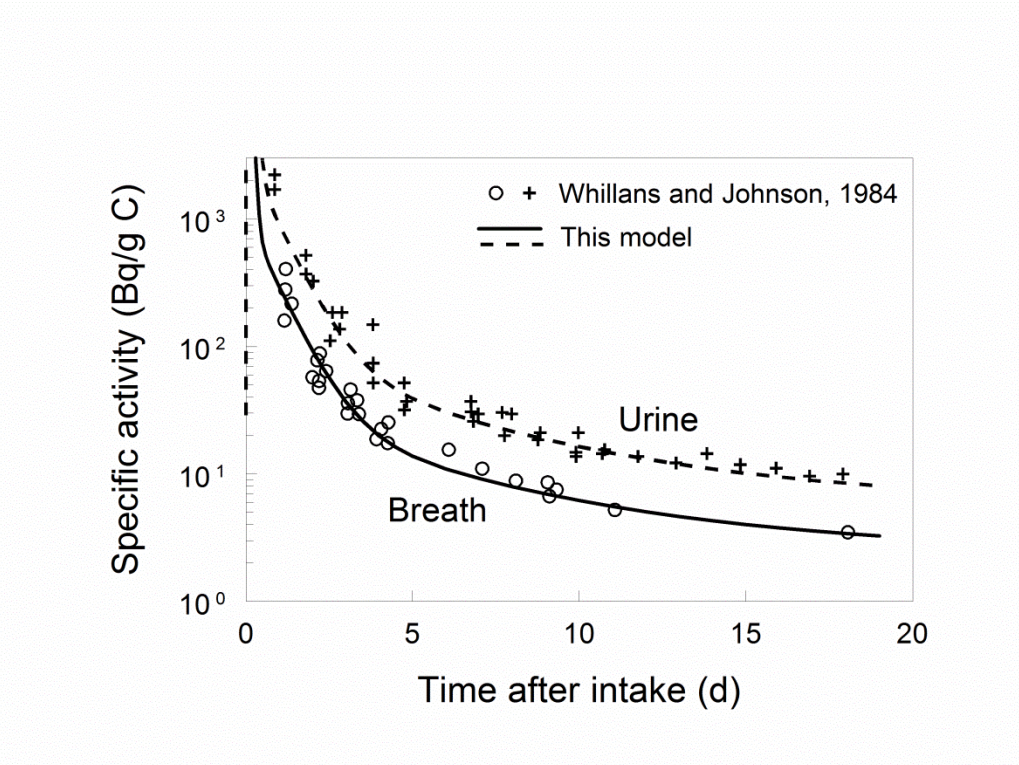

Figure 4. Observations (Whillans and Johnson 1984) and model predictions of exhalation and urinary excretion of ^{14}C following inhalation of $^{14}CO_2$. Predicted specific activities based on reference stable C losses of 230 g d^{-1} in breath and 5 g d^{-1} in urine. In the y-axis label, C represents stable carbon in breath or urine.

Figure 5 compares observations and model predictions of the time-dependent exhalation of ^{14}C following intravenous injection of ^{14}C-bicarbonate, The dashed curve in Figure 5 representing typical observations is based on data from a nutrient oxidation study involving intravenous administration of ^{14}C-bicarbonate to 13 healthy subjects (Winchell et al. 1970). The curve was generated using a two-compartment model of Winchell et al., with mean transfer coefficients calculated from 13 sets of transfer coefficients derived by those investigators by fitting subject-specific data. Inter-subject variability in the transfer coefficients determined by Winchell and coworkers was modest. As illustrated in Figure 6, however, considerable inter-subject variability in the rate of exhalation of the carbon label has been observed in some human nutrient oxidation studies involving administration of labeled bicarbonate, particularly studies with relatively long observation periods.

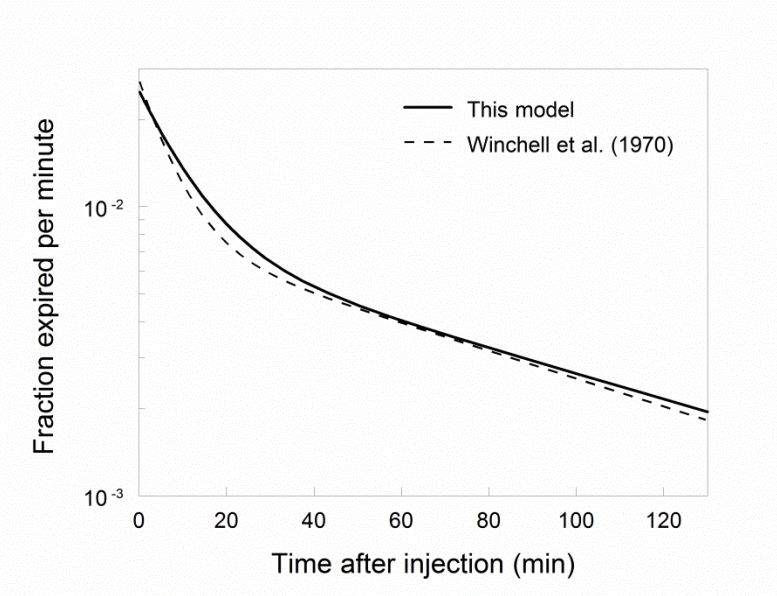

Figure 5. Comparison of model predictions of exhaled ^{14}C with central estimates indicated by data of Winchell et al. (1970) for subjects administered ^{14}C-bicarbonate intravenously.

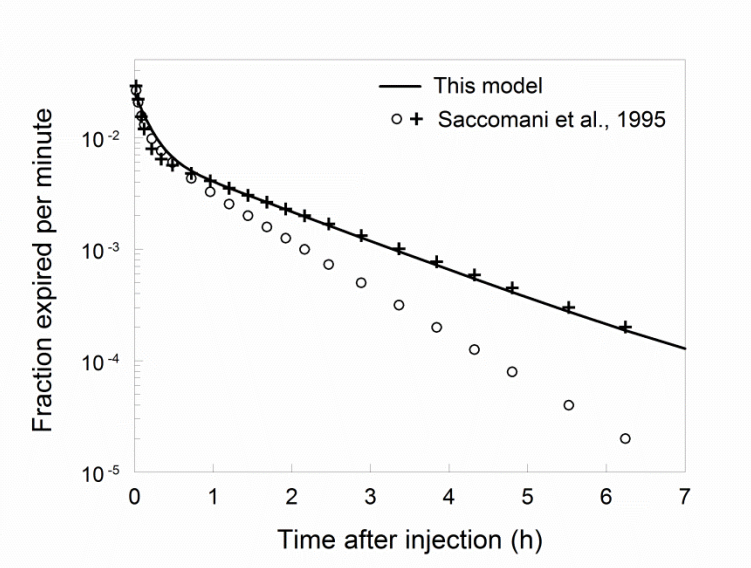

Figure 6. Illustration of subject-specific differences in the exhaled carbon label in nutrient oxidation studies involving intravenous administration of labeled bicarbonate. Plus signs and circles represent observations for two selected subjects of Saccomani et al. (1995).

Figure 7 compares observations and model predictions of loss of ^{14}C in expired air and via skin during continuous infusion with ^{14}C-bicarbonate. The data points represent central values for 6 healthy subjects infused for 36 h and 5 healthy subjects infused for 120 h (Elia et al. 1992, 1995).

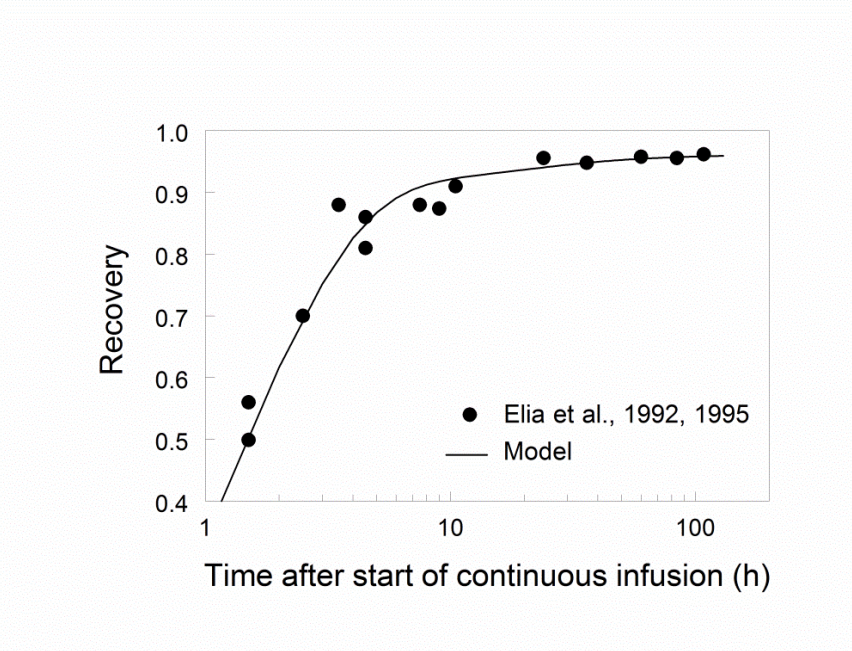

Figure 7. Observations (Elia et al. 1992, 1995) and model predictions of recovery of ^{14}C removed from the body in expired air and skin during continuous infusion with ^{14}C-bicarbonate.

Figure 8 compares model predictions of bone retention of ^{14}C with measured bone retention in rats and mice following intravenous administration of ^{14}C-bicarbonate. These data appear to represent the best available information on bone retention following intake of the forms of carbon of interest here. The animal data were considered as lower bound estimates for humans in view of the higher metabolic rates and bone turnover rates in rats and mice than in humans.

SUMMARY AND CONCLUSIONS

The biokinetic model described here for carbon taken into the human body as carbon dioxide or bicarbonate is a revision of a previously published model (Leggett 2004). The impetus for the earlier model was the need by U.S. radiation protection agencies for an improved dosimetry model for ^{14}C ingested as bicarbonate in drinking water. The earlier model includes compartments depicting an early, rapid exchange of carbon between blood and tissues that are of physiological interest but unimportant for purposes of radiation protection. Rates of excretion via exhaled air, urine, feces, and skin were depicted in the 2004 model, but a limitation of that model with regard to interpretation of bioassay data lies in the depiction of blood carbon as a single, well-mixed pool. Use of a single blood compartment implies that the rate of removal of activity to the urinary bladder contents is at all times parallel to the rate of removal to the environment in expired air. Excretion measurements on human subjects following acute inhalation of $^{14}CO_2$ indicate that this may not the case (Whillans and Johnson 1984), at least during the first day or two after intake. Whillans and Johnson (1984) recommended that assessment of exposure to

$^{14}CO_2$ be conducted at least one day after exposure "because of the rapid changes in activity in breath, and the presence of labile bicarbonate in urine at early times".

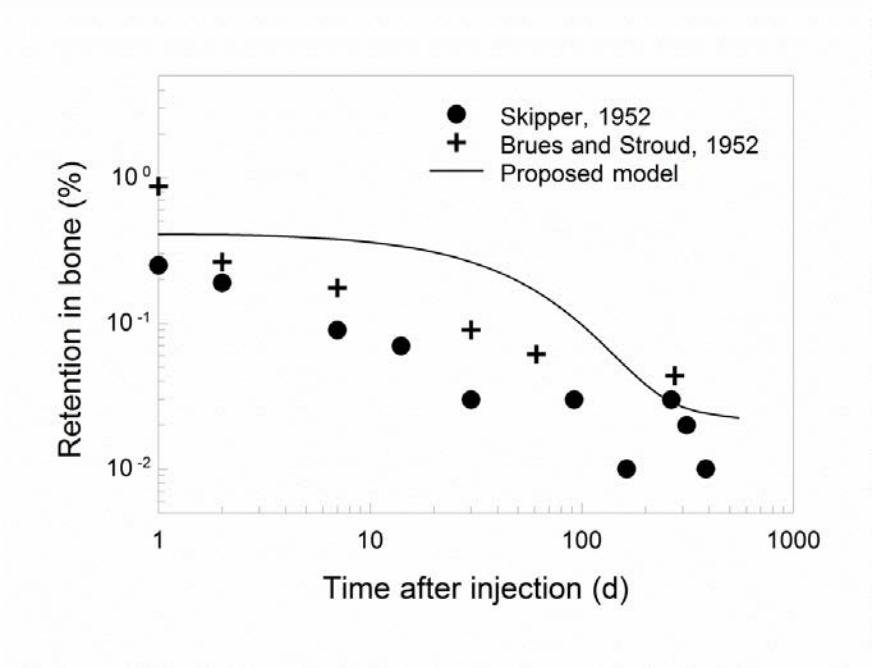

Figure 8. Comparison of ^{14}C retention in bone of rats and mice following intravenous administration of ^{14}C-bicarbonate with predictions for humans. The observations were used as lower-bound estimates for humans due to species differences in metabolic rates.

The model described here improves the 2004 model as a radiation protection tool mainly by: (1) providing a simpler model structure that is more consistent with the biokinetic modeling scheme currently used by the ICRP, (2) achieving closer agreement with observed ^{14}C urinary excretion rates in human subjects at times greater than 24 h after inhalation of $^{14}CO_2$, and yielding more cautious estimates of the relatively uncertain doses to bone surface and red marrow from ^{14}C. The present model reduces the number of tissue compartments from 14 to 8 but adds a blood compartment to the original model structure to allow depiction of non-parallel rates of loss of ^{14}C in expired air and urine as suggested by data for human subjects at early times after inhalation of $^{14}CO_2$ (Whillans and Johnson 1984). The present and original (2004) models yield nearly identical predictions of total-body retention of ^{14}C, but the present model shifts some of the retained activity from soft tissues to bone. As indicated in Figure 9, total-body retention of carbon predicted by the present model (and hence also the 2004 model) following inhalation of carbon dioxide is higher than predicted by the previous ICRP model (Eq. 1 in the Introduction) at times greater than a few hours after intake.

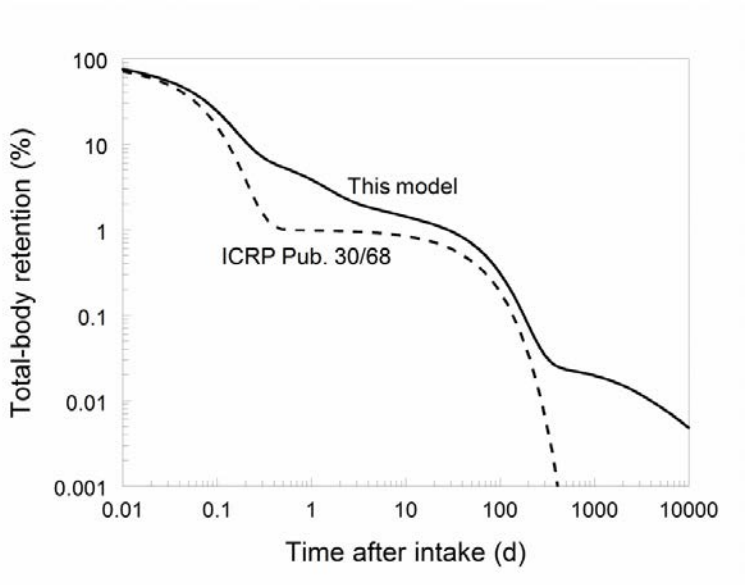

Figure 9. Comparison of predictions of total-body retention of ^{14}C following acute inhalation of $^{14}CO_2$ based on the ICRP's updated and previous (Eq. 1) models for inhaled carbon dioxide.

Table 2 compares predictions of the 50-y integrated activity (total number of nuclear transformations over 50 y following intake) in selected systemic regions based on the updated ICRP model for CO_2 described in this paper and the previous ICRP model (Eq. 1, together with the assumption of uniform distribution in the body). Predictions of the total-body integrated activity based on the previous model are divided into activity in bone and 'other' (total body minus bone) to show that the differences between the two models in predicted integrated activity are mainly due to consideration in the updated model of long-term retention of carbon in bone. The indicated integrated activities in bone and 'other' based on the previous ICRP model are calculated from their reference masses in adult males given in ICRP Publication 89 (2002) and the assumption of uniform distribution of activity in the body.

Table 2. Comparison of 50-y integrated activity in total body, bone, and 'Other' (total body minus bone) for acutely inhaled $^{14}CO_2$, based on the updated and previous ICRP model (Eq. 1 and the assumption of a uniform distribution).

Region	Previous model	Updated model	Update : Previous
Bone	4090[a]	135,300	33
Other	50,140[a]	70,400	1.4
Total body	54,230	205,700	3.8

[a]Based on 5.5 kg bone in a 73 kg male worker (ICRP, 2002).

Table 3. Comparison of effective dose coefficients (Sv Bq^{-1}) for occupational inhalation of $^{14}CO_2$ or ingestion of ^{14}C-bicarbonate, based on the updated and previous ICRP models.

	Effective dose coefficient (Sv Bq^{-1})		
Case	ICRP Pub. 68	Updated model[a]	Ratio Update : Pub. 68
Inhaled $^{14}CO_2$	6.2E-12	2.4E-11	3.9
Ingested ^{14}C-bicarbonate	5.8E-10	3.3E-11	0.057

[a]The dosimetry system of ICRP Publication 68 and the tissue weighting factors of ICRP Publication 60 (1991) were applied to show only the effect due to the change in the biokinetic model.

Table 3 compares the effective dose coefficient for occupational inhalation of $^{14}CO_2$ based on the updated model with the corresponding effective dose coefficient from ICRP Publication 68 (1994), where the retention function shown in Eq. (1) and the assumption of a uniform distribution in the body were applied. The effective dose coefficient listed for the updated model is based on the dosimetry system of ICRP Publication 68 and the tissue weighting factors of ICRP Publication 60 (1991), to show the effect on the effective dose estimate due only to the change in the biokinetic model. The effective dose coefficient based on the updated biokinetic model together with the ICRP's updated dosimetry system is about twofold greater than the value given in ICRP Publication 68.

The updated biokinetic model for inhaled carbon dioxide may also be applied as a systemic model to derive an effective dose coefficient for occupational ingestion of ^{14}C-bicarbonate. The ICRP's effective dose coefficient based on a generic systemic model for carbon has commonly been used for that purpose. That model, introduced in ICRP Publication 30, Part 3 (1981) depicts a uniform distribution of absorbed carbon in the body and a retention half-time of 40 d.

The model described in this paper and the earlier version of that model (the 2004 model) predict the same cumulative loss of ^{14}C in urine following inhalation of $^{14}CO_2$ (2% of intake). The two models differ significantly as bioassay models, however, because the revised model predicts roughly a threefold higher urinary excretion rate after 1 d than predicted by the 2004 model (Figure 10).

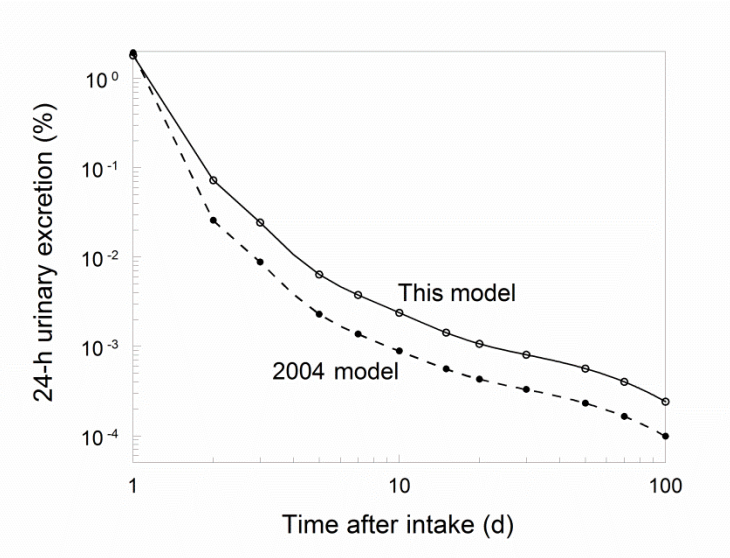

Figure 10. Comparison of predictions of 24-h excretion of ^{14}C following acute inhalation of $^{14}CO_2$, based on the model described in this paper and an earlier version of the model (Leggett 2004). For example, the data point at 1 d represents predicted loss of ^{14}C in urine during the period 0-24 h after intake.

ACKNOWLEDGMENT

The work described in this manuscript was sponsored by the Office of Radiation and Indoor Air, U. S. Environmental Protection Agency (EPA), under Interagency Agreement DOE No. 1824 S581-A1, under contract No. DE-AC05-00OR22725 with UT-Battelle.

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