DOSE COEFFICIENT UNCERTAINTY AND HUMAN VARIATION QUANTIFICATION FEASIBILITY STUDY

Report of Findings in Task 3: Assessment of Primary Dosimetric Data and Previous Studies of Uncertainty and Variability in Radiation Doses

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1. INTRODUCTION

Current dose coefficients for radionuclides are point estimates based on biokinetic models developed from observations of the behavior of elements in the body, together with activity-to-dose conversion models developed from nuclear decay data and anthropomorphic phantoms. These models are intended to represent typical members of the exposed population or specific subgroups of the population such as adults or infants. Tabulations of dose coefficients do not include information on the potential errors in dose coefficients as estimators for typical members of the population or human variation in dose per unit exposure to radionuclides.

The purpose of the present project is to determine the feasibility of a comprehensive characterization of uncertainties in radiation dose coefficients as central estimators and the variability of dose per unit exposure. A critical task in this feasibility study (Task 3 in the Scope of Work) is to assess the quality and completeness of primary biokinetic and dosimetric data available to estimate dose from exposure to key radionuclides and identify available resources for characterizing uncertainty and variability in dose per unit intake.

Assessments have been performed for important isotopes of 15 elements: H (as tritiated water), C (as inhaled carbon dioxide or ingested bicarbonate), Co, Sr, Zr, Ru, Sb, I, Cs, Ir, Po, Ra, Th, U, and Pu. The assessments are summarized in this letter report. Because one of the main purposes of Task 3 is to identify available resources for characterizing uncertainty and variability in dose, the set of elements indicated above was chosen mainly to cover most of the cases in which uncertainty or variability in dose estimates has already been addressed to some extent in the literature. Four elements (C, Ir, Po, and Th) were included to represent the much larger class of radionuclides that has received little or no attention in this regard. Thus, the assessments in this report are skewed toward the more frequently studied cases and should not be interpreted as indicating that uncertainty or variability in dose has been extensively studied for radionuclides in general.

More detailed assessments for a smaller number of radionuclides will be made as part of a subsequent task in this project (Task 4). This small set of radionuclides will be selected mainly to represent different levels of uncertainty (e.g., well understood, moderately well understood, poorly understood, and very poorly understood cases).

2. QUALITY OF PRIMARY DATA USED TO DERIVE DOSE COEFFICIENTS

2.1. Main types of data

To assess the quality of the data underlying current radiation dose coefficients, it is convenient to divide the data into two main categories: biokinetic data used to model the behavior of radionuclides in the human body, and dosimetric data used to model radiation transport and deposition of ionizing energy in tissues.

Biokinetic data give quantitative information on the fate of a radionuclide after its entry into the body through inhalation, ingestion, or other paths. Biokinetic data are used to develop biokinetic models for radionuclides, which are in turn used to predict the time-dependent distribution, retention, and excretion of internally deposited radionuclides.

Dosimetric data include nuclear decay data, anthropomorphic information, and information on the relative biological effectiveness (RBE) of different types of radiation. Nuclear decay data for a radionuclide include its half-life and the types, energies, and yields of emitted radiations. Anthropomorphic data on the masses, densities, and relative positions of organs, tissues, and fluids are used to construct anthropomorphic models. RBEs are based on theoretical calculations and observed comparative effects of a given level of absorbed dose from two different types of radiation on human populations, laboratory animals, or *in vitro* systems.

The nuclear decay data are used together with an anthropomorphic phantom to model radiation transport and deposition of ionizing energy in tissues, for calculation of absorbed dose to tissues both for internally deposited radionuclides and external exposure. The absorbed dose associated with a given type of radiation is multiplied by an RBE to derive an equivalent dose, i.e., dose reduced to a common basis with regard to projected detrimental effects.

The biokinetics of some elements such as strontium, cesium, iodine, radium, and plutonium has been investigated extensively in controlled studies involving human volunteers or laboratory animals, follow-up of persons exposed in the workplace, and environmental studies (ICRP, 1993, 1995a, 1995b). As a whole, however, biokinetic information is much less complete and much less uniformly derived than nuclear decay data. The biokinetics of radionuclides usually represents the most important source of uncertainty and variability in radiation doses from internally deposited radionuclides.

2.2. Quality and completeness of dosimetric data

2.2.1. Internally deposited radionuclides

2.2.1.1. Nuclear decay data

Nuclear decay data reflect a combination of direct measurements made in laboratory studies and application of principles of physics. A number of different nuclear decay databases have been developed by different researchers and organizations, often for application to specific problems. Different databases appear to have been developed in a reasonably uniform and consistent manner. In this pilot study, attention is focused on a few relatively extensive and widely used nuclear data bases.

For many years the dosimetry group at Oak Ridge National Laboratory (ORNL) has maintained machine-readable tabulations of nuclear decay data for use in radiation dose calculations. ORNL data for 820 radionuclides were published in abridged form in

Publication 38 of the International Commission on Radiological Protection (ICRP, 1983), and data for 242 of these radionuclides of importance in nuclear medicine were published in a monograph of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (Weber et al., 1989). The unabridged nuclear decay data used in preparing ICRP Publication 38 and the MIRD monograph are available in electronic form (Eckerman et al., 1994). The ICRP Publication 38 database in unabridged form was used to develop the inhalation and ingestion dose coefficients currently recommended by the ICRP.

The nuclear decay database of ICRP Publication 38 was recently expanded in a joint project of the Japan Atomic Energy Research Institute (JAERI) and ORNL (Endo et al., 2003, 2004). The expanded tabulation, referred to as the JAERI database, addresses 1034 radionuclides. This represents only about a fourth of known radionuclides, but the database includes most radionuclides with estimated half-life greater than 10 min. The half-life of at least 132 radionuclides is not known (Endo et al., 2004).

The JAERI database reflects updated decay information on many of the radionuclides addressed in ICRP Publication 38. The extent of changes in decay data implied by the new information provides insight into the reliability and stability of the existing nuclear decay databases. Comparison of the ICRP Publication 38 and JAERI databases serves to increase our confidence that nuclear decay data are reasonably well characterized overall and usually represent only a modest error in dose coefficients. In several specific cases, however, substantial differences in the JAERI and ICRP Publication 38 databases are evident. For example, estimates of the radiological half-life were changed by 40% or more for some radionuclides (e.g., ^{79}Se, ^{108m}Ag, ^{194}Hg), and energies of emissions from some radionuclides were changed by an order of magnitude or more (e.g., ^{80}Sr) (Endo et al., 2004).

Existing nuclear decay databases do not address all of the radionuclides of importance in occupational, medical, or environmental settings. For example, the Spallation Neutron Source (SNS) now under construction at ORNL will produce a number of radionuclides for which a complete set of nuclear decay data have not yet been assembled (e.g., ^{189}Hg, ^{190}Pb). The incompleteness of the decay data hampers safety analyses for this facility because it limits the accuracy of dose estimates that can be made for accident scenarios. Generally, some decay information is available on each of the SNS-produced radionuclides, including its half-life and mode(s) of decay. In a recent dose assessment for the SNS, the investigators (of the present project) based dose estimates for these radionuclides on surrogate decay data. That is, gaps in nuclear decay data for a radionuclide were filled in using more complete nuclear decay data for another radionuclide with a similar decay mode, usually another isotope of the same element. Sensitivity analyses indicate that this approach will usually result in a fairly modest error (less than a factor of 2) in dose estimates but that larger errors sometimes result. For example, one of the radionuclides addressed in SNS accident scenarios is ^{188}Au ($T_{1/2}$ = 8.84 min). Its chain members are ^{188}Pt ($T_{1/2}$ = 10.2 d) and ^{188}Ir (41.5 h). Reasonably complete nuclear decay data are available for ^{188}Pt and ^{188}Ir but not ^{188}Au. A range of effective dose coefficients for inhalation of relatively insoluble ^{188}Au were calculated

using the JAERI decay data for ^{188}Pt and ^{188}Ir together with energies and yields from that database for each of a set of surrogates for ^{188}Au: ^{186}Au, ^{190}Au, ^{191}Au, ^{192}Au, ^{193}Au, ^{194}Au, ^{195}Au, and ^{196}Au. Derived dose coefficients varied by a factor of 4.7, from 3.0×10^{-12} to 1.4×10^{-11}, with 6 of the 8 values falling between 4.0×10^{-12} and 8.0×10^{-12}.

To summarize, nuclear decay data for radionuclides have been developed in a reasonably uniform manner by researchers worldwide. These data represent a combination of direct measurements and application of principles of physics. Decay data for most radionuclides do not appear to represent a major source of uncertainty in dose coefficients, but sizable errors in half-lives as well as energies and yields of emissions have been identified in recent years for several radionuclides. Moreover, a number of radionuclides of potential importance in occupational, medical, or environmental settings are not addressed in any of the current databases. Surrogate nuclear decay data can be applied to radionuclides with missing decay data, but sensitivity analyses indicate that this could sometimes result in sizable errors in dose estimates.

2.2.1.2. Anthropomorphic phantoms

Nuclear decay data are used together with anthropomorphic phantoms to derive a quantity called the specific effective energy (SEE). For a given source organ S (organ containing the activity of interest) and target organ T (organ for which the dose is calculated), the quantity SEE(T,S) reflects the yield, average energy, and radiation weighting factor for each type of radiation emitted from S as well as its specific absorbed fraction SAF(T,S). The specific absorbed fraction SAF(T,S) for a radiation type is the fraction of energy emitted from S that is absorbed by T per unit mass of T.

Numerous anthropomorphic phantoms have been developed over the years for use in radiation dosimetry. Many of these have been developed for application to specific populations such as Japanese or Korean populations (Saito et al., 2001; Lee et al., 2004).

There are two main types of anthropomorphic phantoms currently in use in radiation protection. These are referred to as mathematical phantoms and voxel phantoms. In mathematical phantoms, the size and shape of an organ or tissue is approximated by a three-dimensional figure such as a portion of a sphere, cylinder, or cone, that can be represented by a relatively simple mathematical expression involving positional variables x, y, and z. A voxel phantom is based on computed tomographic data for a real person, with each organ, tissue, or fluid represented as a set of points describing its volume and position as determined in the scan. A voxel phantom is typically based on a living adult who is undergoing a scan for medical purposes but sometimes is based on a cadaver.

A voxel phantom based on a living person is more realistic than a mathematical phantom in the sense that it accurately represents the sizes and relative geometries of tissues of a real person in a real position. Uncertainties arise in applications of a voxel phantom to individuals or to a population due to variation in organ size and shape from one person to another or one position to another. Also, the resolution of voxel phantoms (down to about 3 mm) is not sufficient to address some target regions within the lungs and skeleton

with dimensions of a few microns. For this reason it has been necessary to incorporate some features of mathematical phantoms into voxel phantoms to address short-range radiations including alpha and beta particles and discrete electrons.

Information on the sizes and relative geometries of some source and target regions in the respiratory tract and skeleton is not sufficient to model irradiation from beta particles, discrete electrons, and low-energy photons with high accuracy, regardless of the type of phantom applied. In the respiratory tract, for example, there are narrow layers of radiosensitive basal and secretory cells in the epithelium that may be irradiated by beta particles and discrete electrons emanating from radionuclides contained in the nearby gel layer, the sol layer, and other source "compartments" within the epithelium. Radiosensitive skeletal tissues include the red bone marrow, which lies within the generally tiny cavities of trabecular bone, and osteogenic cells adjacent to the surfaces of both cortical and trabecular bone. For the red bone marrow the pertinent dose is assumed to be the average dose to the marrow space within trabecular bone. For the osteogenic tissue, the equivalent dose is calculated as an average over tissues up to a distance of 10 μm from the relevant bone surface. In the vicinity of discontinuities in tissue compositions such as that between bone mineral and red bone marrow, the assumption that the skeleton is a uniform mixture of its component tissues can lead to sizable errors in estimates of dose from beta particles, discrete electrons, and low-energy photons. For example, neglect of energy transferred to electrons by photon interactions in these regions can result in overestimates of dose to bone marrow by as much as 300-400% for photon energies less than 100 keV. Similarly, conventional methods for treating beta emissions in the skeleton may substantially overestimate the dose to soft tissues of the skeleton.

Inhalation and ingestion dose coefficients currently recommended by the ICRP are based on mathematical phantoms (Cristy and Eckerman, 1987). Voxel phantoms for a reference adult male and a reference adult female are currently under development for use by the ICRP. It has been necessary to adjust the height of the phantoms and organ sizes for consistency with characteristics (e.g., organ masses) of the ICRP's reference adult males and females given in ICRP Publication 89 (2002). In the absence of suitable age-specific voxel phantoms, it is expected that the ICRP's current mathematical phantoms for children will continue to be used for age-dependent dosimetry.

Voxel models can be used to investigate inter-subject variability in SEE values and also provide a check on the accuracy of dose estimates based on mathematical phantoms (Zankl et al., 2002, 2003). According to Zankl et al. (2003), calculations based on seven voxel models derived from seven different adult subjects, some male and some female, indicate that anatomical differences can lead to order-of-magnitude variations in SAFs for low photon energies. Sizable differences between dose estimates for mathematical and voxel phantoms also are seen for low photon energies since the inter-organ distances tend to be larger in the mathematical phantoms than in reality due to simplification of organ shapes. Differences in SAFs between different types of phantoms or between two different voxel phantoms decrease with increasing energy and disappear for high-energy photons such as emissions from ^{60}Co or ^{192}Ir.

In most cases, alpha and beta particles and discrete electrons will be absorbed in the organ in which they originate (i.e., the source organ, S), so that SAF(S,S) is the inverse of the mass of organ S and SAF(S,T) = 0 if the source organ S is different from the target organ T. Exceptions occur when S and T are separated by only a few microns, which can occur for source and target tissues within the respiratory tract or skeleton. In the respiratory tract, there are narrow layers of radiosensitive basal and secretory cells in the epithelium, and these are irradiated to some extent by beta particles and discrete electrons emanating from nearby source regions including the gel layer and other layers within the epithelium. Irradiation of nearby tissues by beta particles and discrete electrons is also an issue for dose estimates to the red marrow from radionuclides in the complex network of trabecular bone containing the marrow. Finally, the extent of irradiation of bone surface cells from alpha emitters deposited in nearby skeletal sites is not known with much precision.

2.2.1.3. RBEs for alpha particles

Radiobiological data indicate that high-LET alpha radiation has a larger biological effect than an equal absorbed dose of low-LET radiation. Multiplicative factors called RBEs (for relative biological effectiveness) are used to convert absorbed dose from a given radiation type into an "equivalent dose". The ICRP currently applies a factor of 1 for gamma, beta, or electron radiation, 20 for alpha radiation, and 5-20 for spontaneous fission neutron radiation, depending on the energy.

RBEs for alpha particles can be estimated from studies of human populations or laboratory animals internally exposed to alpha emitting radionuclides, *in vitro* data, and theoretical considerations (NCRP, 1990). Ranges of estimated values for alpha particle RBE or neutrons are wide, depending on both the biological system and the observed endpoint (NCRP, 1990; Eckerman et al., 1999). The uncertainty in the RBE estimated from an individual study also is usually large, primarily due to the uncertainty in extrapolation of low-LET data to low doses. At relatively high doses, the effectiveness of alpha emitters has been found to be 15 to 50 times that of beta emitters for the induction of bone sarcomas, liver chromosome aberrations, and lung cancers (NCRP, 1990). Since the LET of secondary protons produced by fission neutrons in living tissue is comparable to that for alpha particles, data on the RBE of fission neutrons provides ancillary information relevant to the estimation of alpha particle RBE. Where the dose response data on carcinogenic endpoints are adequate to derive an estimate, fission neutrons have been found to have an RBE between 6 and 60 times that of low dose gamma rays (NCRP, 1990). Overall, experimental data for solid tumor induction with alpha particles and fission neutrons suggest a central value of about 10-30 and a range of roughly 5 to 60 for the RBE relative to low-dose, low-LET radiation (NCRP, 1990; Eckerman et al., 1999).

The problem also arises that the effective RBE may vary with cancer type or cancer site. Site-specific cancer risk estimates for alpha particles have been calculated using human epidemiological data on low-LET radiation such as in the Atomic Bomb Survivor Study and laboratory data on the RBE of high-LET radiation compared to a reference low-LET

radiation (NCRP, 1990). There is evidence that the RBE of 20 commonly applied to alpha particles is much too high with regard to radiogenic leukemia. In Federal Guidance Report No. 13 (Eckerman et al., 1999), an RBE of 1 was applied to alpha-particle irradiation of red marrow.

2.2.2. External dose

2.2.2.1. Nuclear decay data and anthropomorphic phantoms

The nuclear decay data and anthropomorphic phantoms applied to internally deposited radionuclides are also used to derive dose coefficients for external exposure. For example, the ICRP Publication 38 database and mathematical phantoms used to develop the inhalation and ingestion dose coefficients currently recommended by the ICRP were also used to derive the external dose coefficients tabulated in Federal Guidance Report No. 12 (Eckerman and Ryman, 1993).

As is the case for internally deposited radionuclides, voxel phantoms can be used to investigate variability in external dose and provide a check on the accuracy of external dose estimates based on mathematical phantoms. Zankl et al. (2002) used seven adult male and female voxel models to examine differences (essentially, inter-subject variability) of dose coefficients for external whole body irradiation by photons of energies between 10 keV and 10 MeV. The idealized geometries considered were broad parallel photon beams in anterior-posterior, posterior-anterior, left- and right-lateral direction and a full 360 degree rotation around the body length axis. Dose differences between the different voxel models were below 30% for some organs and geometries for photon energy between 60 and 200 keV but were 100% or more in some cases due to differences in stature and individual anatomical details. According to the authors, the interindividual differences in body size and organ geometry could amount to several hundred per cent for low photon energies. Comparison with estimates based on mathematical models indicated differences of several tens of per cent for some organs.

2.2.2.2. RBEs for neutrons

Radiobiological data indicate that neutrons as well as alpha particles have a larger biological effect than an equal absorbed dose of low-LET radiation, that is, the RBE is greater than 1. The uncertainty in the RBE from neutrons is a source of uncertainty in external dose from some sources. Experimental data as well as theoretical considerations indicate that the neutron RBE depends on energy. Where the dose response data on carcinogenic endpoints are adequate to derive an estimate, fission neutrons have been found to have an RBE of 6-60 times that of low dose gamma rays (NCRP, 1990).

2.3. Quality and completeness of biokinetic data

2.3.1. Definitions and notation

"Biokinetic data" refers to observations of the absorption, distribution, retention, and excretion of substances, particularly radionuclides or elements, after entry into the body. Biokinetic data are used to construct biokinetic models that in turn are used to predict the time-dependent distribution of activity in the body and its rate of excretion. The predictive reliability of a biokinetic model depends on the quality and completeness of the underlying biokinetic data.

In contrast to nuclear decay data, biokinetic data for elements or specific radionuclides have been derived and reported in a wide variety of forms, and this hampers the development of uniform databases. Moreover, qualitative physiological information generally is required for proper interpretation of quantitative biokinetic data developed for a specific characteristic of an element or radionuclide. To avoid the loss of critical qualitative information in applications of the data, qualitative information should be an integral part of a biokinetic database.

This section describes the quality of the current biokinetic databases for selected elements or, in two cases, compounds. Biokinetic data for each case are divided into information on: (1) distribution and retention in the respiratory tract and absorption from the respiratory tract to blood; (2) fractional absorption from the gastrointestinal tract to blood; and (3) the systemic biokinetics, i.e., behavior in the body after absorption to blood from the respiratory or gastrointestinal tract. The following information is given under each of these topics:

Reviews or bibliographies: No attempt is made in this summary report to provide a complete bibliography. Rather, best available modern reviews or bibliographies on the topic are cited as starting places for development of a comprehensive bibliography and a complete biokinetic database.

Main types of biokinetic data for modeling: The following abbreviations are used for different types of biokinetic data for an element or compound:

- H1: direct information on humans, i.e., quantitative measurements of the substance in human subjects;
- H2: observations of the behavior of chemically similar and/or physiologically related substances in human subjects;
- A1: observations of the behavior of the substance in non-human species
- A2: observations of the behavior of chemically similar and/or physiologically related substances in non-human species;
- P: Physiological information, e.g., the turnover rate of water in the body as one estimate of the retention time of tritium taken into the body as tritiated water, or the turnover rate of cortical or trabecular bone as an estimate of the retention time of plutonium in bone of that type;
- *in vitro* data

The notation X > Y indicates that both data types X and Y are available, that data type X represents the more valuable source for modeling purposes, and that Y is used to supplement X in model development. The notation X >> Y means that data type X is considerably more important than Y. The notation X ~ Y indicates that the two data types are roughly of equal value for purposes of constructing a biokinetic model.

Quality of biokinetic data: The letters A, B, C, and D are used to grade the available information. "A" indicates high-quality, reasonably complete data that provide a good understanding of the biokinetics of the element. "B" indicates that available data are of reasonably high quality but are incomplete in ways that decrease confidence in derived dose coefficients. "C" indicates still weaker data with more important gaps or greater inconsistencies than a "grade B" database. "D" indicates that the database is sparse, highly inconsistent, and/or of questionable reliability.

Comments: Brief comments are given to summarize major strengths or weaknesses of the biokinetic database for the substance.

2.3.2. Summary of biokinetic databases for selected elements or compounds

2.3.2.1. Antimony

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b
Main types of biokinetic data for modeling: A1 >> H1
Quality of biokinetic data: C
Comments: Data are available on occupational exposure to antimony compounds but do not provide a firm basis for categorizing solubility in the lungs. More precise inhalation data are available for rodents and dogs, but application to humans is uncertain due to recognized species differences in the biokinetics of antimony.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1995a; Harrison et al., 2001
Main types of biokinetic data for modeling: A1 >> H1
Quality of biokinetic data: C
Comments: Absorption of antimony is difficult to estimate from available information due to dependence on chemical form and animal species.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1995a; Leggett et al., 1998
Main types of biokinetic data for modeling: A1 >> H1
Quality of biokinetic data: C
Comments: Animal data are difficult to interpret due to dependence on chemical form, route of administration, and animal species. Human data are mainly from environmental studies and are of questionable reliability due to difficulties in measuring low levels of antimony in food and human tissues.

2.3.2.2. Carbon (as CO_2 or HCO_3^-)

Behavior in respiratory tract (C inhaled as CO_2)

Reviews or bibliographies: ICRP, 1995b
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A
Comments: The behavior of CO_2 in the respiratory tract is reasonably well characterized. Absorption to blood is rapid and nearly complete (i.e., nearly 100%).

Fractional uptake from gastrointestinal tract (C ingested as HCO_3^-)

Reviews or bibliographies: ICRP, 1989
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A
Comments: Gastrointestinal uptake of bicarbonate appears to be nearly complete.

Systemic biokinetics (C reaching blood as CO_2 or HCO_3^-)

Reviews or bibliographies: ICRP, 1989; Leggett, 2004
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A – for early to intermediate times; B – for times greater than a few months after uptake to blood
Comments: Bicarbonate and carbon dioxide are largely reduced to a common form after entering blood and thus can be assumed to have the same systemic biokinetics. The fate of absorbed carbon during the first few weeks after administration is known reasonably well from studies of human subjects injected with labeled bicarbonate or inhaling labeled carbon dioxide. Data on laboratory animals administered labeled forms of carbon provide information on the tissue distribution and long-term retention of carbon. Different ICRP models for inhaled $^{14}CO_2$ have given rise to considerably different dose coefficients due to subtle problems with model structure.

2.3.2.3. Cesium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 ~ A1
Quality of biokinetic data: A
Comments: Most common forms of cesium are readily soluble in the lungs. Cesium associated with irradiated fuel fragments shows mixed behavior, with much of the inhaled cesium rapidly absorbed to blood and the rest absorbed over a period of months or longer.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1989; Harrison et al., 2001; EULEP, 2004
Main types of biokinetic data for modeling: H1
Quality of biokinetic data: A

Comments: Most human studies show virtually complete absorption of cesium ingested cesium in soluble form. Cesium appears to be slightly less available for absorption if incorporated into meat and considerably less available in fallout or irradiated reactor fuel particles.

Systemic biokinetics

Reviews or bibliographies: Leggett et al., 2003
Main types of biokinetic data for modeling: H1 > H2 ~ A1 >A2
Quality of biokinetic data: A
Comments: Cesium is one of the best understood elements with regard to systemic biokinetics due to a large database for human subjects as well as non-human species. A fairly regular pattern of physiological discrimination among the chemically similar elements cesium, potassium, and rubidium allows the use of combined databases for these three elements (i.e., chemical analogy) in the development of a highly detailed biokinetic model for cesium.

2.3.2.4. Cobalt

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 ~ A1
Quality of biokinetic data: A
Comments: The behavior of inhaled cobalt in the respiratory tract has been investigated in human volunteers and a variety of animal species including baboons and dogs.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1993; Harrison et al., 2001; EULEP, 2004
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: B
Comments: Although there have been several studies of gastrointestinal absorption of cobalt, determination of typical absorption is complicated by high inter- and intra-subject variability and variation with age, gender, chemical form, and animal species.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1993; Leggett et al., 1998
Main types of biokinetic data for modeling: H1 ~ A1
Quality of biokinetic data: B
Comments: Whole-body retention of inorganic cobalt by the adult can be estimated with reasonably high confidence from results of human studies. Information on the systemic distribution of cobalt comes mainly from studies on laboratory animals, and apparent species differences in the behavior of cobalt complicate extrapolation of these data to man.

2.3.2.5. Hydrogen (as tritiated water, HTO)

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b
Main types of biokinetic data for modeling: H1 > A1 > *in vitro* data
Quality of biokinetic data: A
Comments: The behavior of HTO in the respiratory tract appears to be reasonably well characterized. The data indicate that inhaled HTO is rapidly and nearly completely absorbed to blood.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1989; Harrison et al., 2001
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A
Comments: Gastrointestinal uptake of tritium as HTO appears to be well characterized. Typically, HTO is nearly completely absorbed to blood.

Systemic biokinetics

Reviews or bibliographies: ICRP,1989; Hill and Johnson, 1993; Leggett et al., 1998
Main types of biokinetic data for modeling: H1 > P > A1
Quality of biokinetic data: A – for early to intermediate times; B – for times greater than a few weeks or months after exposure
Comments: Tritium is known to be fairly uniformly distributed in the body. Human as well as animal data indicate that retention can be described in terms of three first-order components. The dominant, short-term component closely approximates the turnover of body water, and reasonably consistent estimates for the half-time of this component have been determined in a number of studies. The sizes and half-times of the longer-term components are not known with much precision, but available information yields bounds on these components (they represent at most a few percent of absorbed tritium and their half-times are at most a few hundred days) and indicates that they are relatively minor contributors to radiation dose. The equivalence of the short-term component with the turnover of body water, as supported by observations on adult male humans and laboratory animals of various ages, provides a means of extending the model to children and adult females.

2.3.2.6. Iodine

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A
Comments: Iodine inhaled in most commonly encountered forms is rapidly absorbed to blood.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1989; Harrison et al., 2001

Main types of biokinetic data for modeling: H1
Quality of biokinetic data: A
Comments: Typically, absorption of iodide from the gastrointestinal tract is virtually complete.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1989; Berkovski, 1999
Main types of biokinetic data for modeling: H1
Quality of biokinetic data: A
Comments: Reported thyroidal uptake fractions and biological half-times are highly variable, due largely to a strong dependence of the biokinetics of absorbed radioiodine on the level of stable iodine in the thyroid. Large differences in values reported by investigators from different countries have been attributed to the high variability in the concentration of iodine in foods in different countries, but substantial variability in thyroidal uptake fractions and biological half-times is also seen among members of the same population. For example, in six normal male subjects (mean age 40 +/- 7 y) from the same area of the U.S., estimated uptake of radioiodine by the thyroid varied by a factor of 2 and the biological half-time in the thyroid varied from 27 d to more than 200 d (van Dilla and Fulwyler, 1963).

2.3.2.7. Iridium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1980
Main types of biokinetic data for modeling: A1 >> H1
Quality of biokinetic data: D
Comments: Very limited data are available on occupational exposure to an unknown form of iridium. Some inhalation data are available for rodents.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1980
Main types of biokinetic data for modeling: A1
Quality of biokinetic data: D
Comments: Absorption of ^{192}Ir administered as $Na_2{}^{192}IrCl_6$ was measured in mice, rats, monkeys, and dogs in a single study.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1980
Main types of biokinetic data for modeling: A1
Quality of biokinetic data: D
Comments: The systemic biokinetics of iridium has been studied to a limited extent in rats, mice, monkeys, and dogs. Species differences are suggested. Different studies on rats have not given consistent results.

2.3.2.8. Plutonium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1, A1
Quality of biokinetic data: A
Comments: Plutonium is one of the most extensively studied elements with regard to behavior in the respiratory tract.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling:
Quality of biokinetic data: B
Comments: Gastrointestinal absorption of plutonium has been investigated in a number of studies involving human subjects or laboratory animals. Precise determination of the level of absorption is difficult because absorption is extremely low and variable.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1993; Leggett, 2003.
Main types of biokinetic data for modeling: H1 > A1 > H2~A2
Quality of biokinetic data: A
Comments: The systemic biokinetics of plutonium is reasonably well characterized on the basis of injection data for human volunteers, bioassay and autopsy data on plutonium workers, and numerous studies of the fate of inhaled, ingested, or injected plutonium in laboratory animals.

2.3.2.9. Polonium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; Leggett and Eckerman, unpublished report
Main types of biokinetic data for modeling: H1 ~ A1
Quality of biokinetic data: B
Comments: Most commonly encountered forms of polonium appear to be moderately soluble in the respiratory tract.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1993; Leggett and Eckerman, unpublished report
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: B
Comments: Polonium incorporated into food appears to be more readily absorbed than inorganic forms generally encountered in industry.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1993; Leggett and Eckerman, 2001
Main types of biokinetic data for modeling: H1 ~ A1

Quality of biokinetic data: B
Comments: Interpretation of the data is complicated by an apparent dependence on chemical form, route of exposure, and animal species. The reliability of much of the occupational data on urinary excretion of polonium is in question.

2.3.2.10. Radium

Behavior in respiratory tract
Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 ~ A1 > *in vitro*
Quality of biokinetic data: B
Comments: Available information suggests that most radium compounds are soluble or moderately soluble in the lungs.

Fractional uptake from gastrointestinal tract
Reviews or bibliographies: ICRP, 1993; Harrison et al., 2001
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A
Comments: Confidence in various estimates of radium absorption is gained from the consistency of the data for human subjects. Absorption appears to be greater in humans than in non-human species that have been studied.

Systemic biokinetics
Reviews or bibliographies: Leggett, 1992; Leggett et al., 1998; ICRP, 1993
Main types of biokinetic data for modeling: H1 > H2 >A1 > A2 > *in vitro*
Quality of biokinetic data: A
Comments: The biokinetics of radium has been studied extensively in human subjects and laboratory animals. Findings for radium are supported by information for its close physiological analogue, barium, as well as for the chemical analogues strontium and calcium. Animal data provide additional details but must be used with care due to species dependence in some aspects of radium biokinetics.

2.3.2.11. Ruthenium

Behavior in respiratory tract
Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: B
Comments: Information from controlled studies is limited. Data from occupational exposures suggest that ruthenium compounds inhaled as particulates vary from moderately soluble to relatively insoluble in the respiratory tract.

Fractional uptake from gastrointestinal tract
Reviews or bibliographies: ICRP, 1989; Harrison et al., 2001; EULEP, 2004
Main types of biokinetic data for modeling: H1 ~ A1
Quality of biokinetic data: B

Comments: Although gastrointestinal uptake of ruthenium has not been extensively studied, results from available studies are reasonably consistent and indicate uptake of at most a few percent of ingested ruthenium.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1989; Leggett et al., 1998
Main types of biokinetic data for modeling: A1 > H1
Quality of biokinetic data: C
Comments: Knowledge of the biological behavior of ruthenium comes mainly from studies on mice, rats, guinea pigs, rabbits, cats, dogs, and monkeys. Limited information for human subjects is broadly consistent with the animal data.

2.3.2.12. Strontium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 ~ A1
Quality of biokinetic data: B
Comments: Available information suggests that most strontium compounds are readily soluble in the lungs, but highly insoluble strontium compounds have been encountered.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP 1993; Harrison et al., 2001; Apostoaei and Miller, 2004; EULEP, 2004
Main types of biokinetic data for modeling: H1
Quality of biokinetic data: A
Comments: Absorption depends on age, the level of calcium in diet, and the type of food in which strontium is ingested.

Systemic biokinetics

Reviews or bibliographies: Leggett, 1992; ICRP, 1993; Leggett et al., 1998
Main types of biokinetic data for modeling: H1 > H2 > A1 > A2 > *in vitro*
Quality of biokinetic data: A
Comments: A large biokinetic database related to the transfer of ^{90}Sr from food and milk to the human skeleton was developed in the 1950s and 1960s. Human data are also available from a number of controlled human studies. Considerable biokinetic data is available for calcium, which is a close physiological analogue of strontium, and for other alkaline earth elements. The biokinetics of strontium, calcium, and other alkaline earths has also been investigated extensively in animal studies.

2.3.2.13. Thorium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: A1 > H1

Quality of biokinetic data: B
Comments: Available data suggest that most commonly encountered thorium compounds are moderately soluble or relatively insoluble in the lungs.

Fractional uptake from gastrointestinal tract
Reviews or bibliographies: ICRP, 1995a
Main types of biokinetic data for modeling: H1, A1
Quality of biokinetic data: C
Comments: Information on gastrointestinal uptake of thorium is less complete than that for some other actinide elements. Available information suggests that absorption of thorium as well as other actinide elements except uranium is extremely low, on the order of 0.05%.

Systemic biokinetics
Reviews or bibliographies: ICRP, 1995a; Leggett, 1997
Main types of biokinetic data for modeling: H1 ~ A1 > H2, A2
Quality of biokinetic data: B
Comments: The biokinetics of thorium appears to be broadly similar to that of other actinide elements excluding uranium. The database for thorium is considerably smaller than that for some other actinides, and chemical analogy is used to model some aspects of thorium biokinetics.

2.3.2.14. Uranium

Behavior in respiratory tract
Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A
Comments: The distribution, retention, and absorption of inhaled uranium have been investigated extensively in workers and laboratory animals.

Fractional uptake from gastrointestinal tract
Reviews or bibliographies: ICRP, 1995; Leggett and Harrison, 1995
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: A-
Comments: Information on gastrointestinal absorption of uranium is available from controlled studies involving human volunteers and from dietary balance data for several different groups of humans. The various studies give reasonably consistent estimates of absorption, usually on the order of 1-2% of the ingested amount.

Systemic biokinetics
Reviews or bibliographies: ICRP, 1993; Leggett, 1994
Main types of biokinetic data for modeling: H1 > A1
Quality of biokinetic data: B

Comments: The level of retention of uranium in tissues other than kidney, skeleton, and liver is not well established. Deposition of uranium in the skeleton depends strongly on the rate of bone formation.

2.3.2.15. Zirconium

Behavior in respiratory tract

Reviews or bibliographies: ICRP, 1995b; EULEP, 2004
Main types of biokinetic data for modeling: A1 > H1
Quality of biokinetic data: C
Comments: Observations of the fate of inhaled zirconium generally represent measurements of the combined activity of ^{95}Zr ($T_{1/2}$ = 64 d) and its daughter ^{95}Nb ($T_{1/2}$ = 35 d) and depend on the technically convenient but uncertain assumption that the behavior of niobium is similar to that of zirconium.

Fractional uptake from gastrointestinal tract

Reviews or bibliographies: ICRP, 1989; Harrison et al., 2001
Main types of biokinetic data for modeling: A1 and A2
Quality of biokinetic data: D
Comments: Different animal studies give inconsistent values for absorption but generally indicate that zirconium is not readily absorbed from the gastrointestinal tract.

Systemic biokinetics

Reviews or bibliographies: ICRP, 1989; Leggett et al., 1998
Main types of biokinetic data for modeling: A1, A2 > H1
Quality of biokinetic data: D
Comments: Direct information on the biokinetics of zirconium in man is very limited. The best available animal data are for rats, mice, and guinea pigs. These data indicate that bone is a major repository, but the data are highly variable and do not reveal a clear distribution between bone and soft tissues or a precise pattern of excretion of zirconium. Due to the paucity of human data and the scatter in animal data for zirconium, there is increased reliance on chemical analogy in this case. Relatively detailed and easily interpreted biokinetic data on hafnium, a close chemical analogue of zirconium, have been developed for rats, hamsters, and marmosets.

3. PREVIOUS STUDIES OF UNCERTAINTY AND VARIABILITY IN RADIATION DOSES

3.1. Common approaches

3.1.1. Comparison of model predictions with independent observations

Comparison of model predictions with independent observations is commonly referred to as "model validation", but the term “matching of history” may be more appropriate. The term “model validation” can be misleading because the independent observations often apply only to limited or dosimetrically unimportant aspects of a model and sometimes involve uncertainties as large as those associated with model predictions. For example, the observations may not be representative of the population of interest or relevant to the conditions addressed by the model, or they may involve sizable errors because of inaccuracies in the measurement procedure. Whatever name is used, comparison of model predictions with carefully determined, relevant, model-independent observations can be a useful, enlightening exercise when assessing the reliability of a model.

For many biokinetic and dosimetric models, there are few if any independent observations that can be used to test against model predictions. This is particularly true at the time of model development, because all obviously pertinent observations may have been used in the construction of the model. Thus, more generally applicable approaches to uncertainty analysis are required.

3.1.2. Parameter uncertainty analysis

A widely used method of analyzing the uncertainty associated with a model prediction is to investigate the effect of propagation of uncertainties associated with model components corresponding to observable phenomena. Such investigations commonly take the form of a parameter uncertainty analysis, meaning that a fixed model structure is used and the model components that are investigated are the parameter values. A distribution of possible values is assigned to each parameter or each major parameter in the model, taking into account correlations between parameters. Distributions of model predictions are then produced through random simulation techniques. Thus, a parameter uncertainty analysis is an examination of the sensitivity of model predictions to uncertainties in input parameters.

Parameter uncertainty analysis seems to have gained popularity as a tool for evaluating radiation dose estimates after the appearance of a paper by Dunning and Schwartz (1981) that addressed the “imprecision” in age-specific dose estimates for ingestion of ^{131}I. A number of parameter uncertainty analyses for dose coefficients have since been published in the open literature, although attention has been focused mainly on a relatively small number of radionuclides including ^{3}H, ^{90}Sr, ^{131}I, ^{137}Cs, and ^{239}Pu.

In a recent series of papers, Bolch and coworkers (Bolch et al., 2001; Bolch et al., 2003; Farfan et al., 2003; Huston et al., 2003) applied standard methods of parameter

uncertainty analysis to investigate sensitivity of predictions of the ICRP's current respiratory model to uncertainty or variability in its parameter values. On the basis of literature reviews, probability density functions were assembled for 69 parameters of the respiratory model describing particle deposition, particle clearance, and dosimetry (conversion from activity in the respiratory tract to estimates of dose). They concluded that most of the variability in the dose to a given target region is explained by only a few input parameters. Further review of their work is needed to determine whether the results are actually applicable to *variability* in the population, i.e., differences in doses for different individuals with similar exposures.

Parameter uncertainty analysis may be best suited to phenomena in which the model structure closely reflects the major processes involved and the spread of consequences is dominated by random variables whose distributions are reasonably well understood. Biokinetic models for radionuclides often are not process models. That is, part or all of the structure of a biokinetic model may be determined as a convenient mathematical summary of selected data and may not be intended to represent physiological processes. As a result, it is frequently the case with biokinetic models that there is no physically meaningful guide to the selection of uncertainty distributions for the parameter values. In such cases, the results of a parameter uncertainty analysis may not be meaningful.

Whether or not a model reflects actual processes, the value of a parameter uncertainty analyses is diminished when the model structure oversimplifies the kinetics of a radionuclide. For example, retention in a given organ is generally modeled as a first-order process, often represented by a single exponential term, while in reality there may be different phases of accumulation and loss that cannot be closely approximated by a simple first-order model.

3.1.3. Expert judgment

All approaches to characterizing uncertainties in dose coefficients involve critical subjective judgments at some point in the analysis. For example, parameter uncertainty analysis requires subjective judgments in the selection of a model to be used as the basis for the analysis and in the assignment of uncertainty distributions to individual parameter values. Model validation (matching of history) based on comparison of predictions and independent observations generally requires subjective judgments regarding the accuracy, relevance, and independence of the observations and the implications of the exercise.

The term "expert judgment" is most often used to describe uncertainty studies in which the subjectivity of the exercise has been emphasized (as opposed to being more or less hidden in the methodology) and the subjective judgments are provided by recognized experts with regard to the specific topics under consideration. Expert judgment has been used by different radiation protection organizations to assess uncertainties in radiation dose models or dose coefficients. The expert judgment process takes different forms. One approach is to ask each expert to provide his or her judgments independently, without conferring with the other experts. The experts may be assembled at some point to discuss their opinions and may be given the opportunity to change their opinions after

the group discussion. Another approach is to allow the experts to discuss the data and issues from the outset of the study and to encourage them to reach a consensus opinion. In any case, the rationale leading to the judgment must be given.

In the early 1990s a task group of the ICRP called INDOS (Internal Dosimetry) initiated a kind of expert judgment evaluation of uncertainties in the ICRP's dose coefficients. The Main Commission of the ICRP later decided that the ICRP should not attempt to assess the uncertainties in its recommended values but encouraged members of INDOS to publish their work to that point in the open literature. The editors of the journal Radiation Protection Dosimetry agreed to publish a series of papers based on the work of the INDOS subgroup. Three papers have been published in this series: (1) an overview of the sources of uncertainty in biokinetic models (Leggett, 2001); (2) an assessment of uncertainties in typical gastrointestinal absorption fractions (called f_1 values) for 12 selected radionuclides (Harrison et al., 2001); and (3) a retrospective look at the sources and extent of errors in each of the plutonium models recommended over the years by the ICRP, in view of recent advances in the biokinetic database for this element (Leggett, 2003). A related paper on the reliability (expected predictive accuracy) of the ICRP's systemic biokinetic models (Leggett et al., 1998) had been published before the series was initiated. That paper gave reliability categories for cumulative activity of selected radionuclides in organs: ^{3}H, ^{106}Ru, and ^{137}Cs in the total body; ^{60}Co and ^{125}Sb in the liver; ^{90}Sr and ^{226}Ra in bone volume; ^{239}Pu on bone surface; and ^{95}Zr in total bone.

In the mid-1990s a joint project was conducted by the NRC and the Commission of the European Communities (CEC) for the purpose of developing credible and traceable uncertainty distributions for input variables to their probabilistic accident consequent codes (NRC-CEC, 1997). A procedure was devised to elicit expert judgment regarding uncertainties in the parameter values. Elicitation questions were developed, tested, and clarified. Internationally recognized experts were selected. Probability training exercises were conducted to establish ground rules for the experts' preparation of material and for the formal elicitation process. Experts developed their uncertainty distributions and rationales independently. A meeting was held in which the experts discussed their independent conclusions and rationales and were given the opportunity to change their conclusions before final, private solicitation interviews with individual experts. The main radionuclides considered were ^{90}Sr, ^{131}I, ^{132}Te, ^{137}Cs, ^{144}Ce, and ^{239}Pu. The exposure modes considered were inhalation and ingestion for all radionuclides except ^{132}Te and ^{144}Ce, for which only inhalation was addressed because they were not considered to be important contaminants of food or water supplies.

An expert solicitation session was held as part of an NCRP assessment of the reliability of biokinetic and dosimetric models, parameters, and dose estimates used to assess individual doses for risk assessments (NCRP Commentary No. 15, 1998). Consensus judgments were solicited on the reliability of selected inhalation or ingestion dose coefficients based on the models and methods of ICRP Publication 30 (1979, 1980, 1981, 1988) for application to an adult male or to a special subgroup of the population (e.g., infants or persons with certain diseases). The consensus judgment for a given case was given in terms of reliability categories A, B, C, and D, representing, respectively: well

known (predictive errors generally less than a factor of 3), moderately well known (factor of 5), poorly known (factor of 10), and very poorly known (factor >10). The following radionuclides were considered: ^{3}H, ^{14}C, ^{55}Fe, ^{60}Co, ^{75}Se, ^{90}Sr, ^{95}Zr, ^{95}Nb, ^{106}Ru, ^{103}Pd, ^{123}Sn, ^{125}Sb, ^{131}I, ^{137}Cs, ^{140}Ba, ^{140}La, ^{144}Ce, ^{210}Pb, ^{210}Po, ^{226}Ra, ^{230}Th, ^{234}U, ^{237}Np, ^{239}Pu, ^{241}Am, and ^{244}Cm. Both inhalation and ingestion coefficients were addressed for each radionuclide except ^{3}H, for which only ingestion was considered (reasons not given). The results do not appear to be of value for the present project because the exercise focused on models of ICRP Publication 30, many of which are now obsolete, and because the expert solicitation was performed in a single meeting and opinions were "off-the-cuff", i.e., not based on review or analysis of the available data.

Federal Guidance Report No. 13 (Eckerman et al., 1999) discusses sources of uncertainty in biokinetic, dosimetry, and risk models for radionuclides and provides uncertainty categories, similar to the reliability categories used in NCRP Commentary No. 15 (1998), for selected risk coefficients. The uncertainty statements are essentially expert judgments made after extensive analysis of the sensitivity of estimates to model uncertainties and, in effect, describe the sensitivity of the risk coefficients to selected sources of uncertainty in the underlying biokinetic, dose, and risk models. The study is unusual in that the analysts did not restrict attention to a fixed biokinetic model structure but considered changes in dose estimates if different but equally plausible structures were applied. Federal Guidance Report No. 13 does not specifically address uncertainties in dose estimates.

3.2. Uncertainty or variability studies for selected elements

3.2.1. Antimony

Studies were found that address uncertainties in some components of current biokinetic and dosimetric models for isotopes of antimony. Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of antimony from the gastrointestinal tract are 0.002-0.2 for adults, 0.002-0.4 for age 10 y, and 0.002-0.6 for infants. On the basis of a literature review and limited sensitivity analysis, Leggett et al. (1998) concluded that the ICRP's systemic biokinetic model for antimony has low reliability (potentially order-of-magnitude error) with regard to predicted cumulative activity of ^{125}Sb in the liver, which appears to be an important repository for antimony. Sensitivity analyses performed during the development of Federal Guidance Report No.13 (Eckerman et al., 1999) suggest that dose from inhalation or ingestion of ^{125}Sb cannot be determined with much confidence, but reasonably high confidence can be placed in external dose coefficients for ^{125}Sb.

3.2.2. Carbon (as CO_2 or HCO_3^-)

No useful uncertainty or variability studies were found.

3.2.3. Cesium

Several investigators have addressed uncertainties in biokinetic or dose estimates for intake of cesium, particularly for the case of ingestion of ^{137}Cs (Schwarz and Dunning, 1982; Bogen et al., 1997; NRC-CEC, 1997; Leggett et al., 1998; Eckerman et al., 1999; Harrison et al., 2001; Apostoaei and Miller, 2004). Included among these studies are some parameter uncertainty analyses (Schwarz and Dunning, 1982; Bogen et al., 1997; Apostoaei and Miller, 2004) based on simplistic biokinetic models for cesium. The general conclusion is that cesium is among the best understood elements with regard to biokinetics in the human body and that dose per unit ingestion can be estimated within a factor of 2. The existing studies provide a good starting place for characterization of uncertainties in dose coefficients for ^{137}Cs, particularly for the case of ingestion. These studies should be critically reviewed with regard to implications of the overly simplistic model structures used in the analyses and assumptions concerning the fate of the daughter, ^{137m}Ba, which may migrate rapidly from ^{137}Cs in the body.

3.2.4. Cobalt

Existing studies of the uncertainty in various aspects of the biological behavior or dosimetry of cobalt isotopes will require critical evaluation but appear to provide a useful starting place for assessing uncertainties at least for the case of ingestion dose coefficients for ^{60}Co. Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of cobalt from the gastrointestinal tract are 0.02-0.2 for adults, 0.03-0.5 for age 10 y, and 0.04-0.8 for infants. On the basis of a literature review and limited sensitivity analysis, Leggett et al. (1998) concluded that the ICRP's systemic biokinetic model for cobalt has relatively low reliability (potentially order-of-magnitude error) with regard to predicted cumulative activity of ^{60}Co in the liver. Apostoaei et al. (1998) used parameter uncertainty analysis to assess uncertainties in dose coefficients for ingestion of ^{60}Co on the basis of a simplistic model structure and derived an uncertainty factor (ratio of 97.5th to 50th percentiles of the probability distribution) of about 8 for all tissues. Sensitivity analyses performed during the development of Federal Guidance Report No. 13 (Eckerman et al., 1999) suggest that dose from inhalation or ingestion of ^{60}Co cannot be determined with much confidence but that high confidence can be placed in external dose coefficients for ^{60}Co.

3.2.5. Hydrogen (as tritiated water, HTO)

Studies were found that address uncertainties in some components of current biokinetic and dosimetric models for ^{3}H. Harrison et al. (2001) concluded from a literature review that a high confidence interval for fractional absorption of ^{3}H ingested as tritiated water is 0.9-1.0 for all age groups. On the basis of a literature review and sensitivity analysis, Leggett et al. (1998) concluded that the biokinetics of ^{3}H absorbed to blood as tritiated water is reasonably well understood and that cumulative activity in the total body is known within a factor of 2. Sensitivity analyses performed during the development of Federal Guidance Report No. 13 (Eckerman et al., 1999) suggest that dose from

inhalation or ingestion of ^{3}H as tritiated water can be estimated with reasonably high confidence.

3.2.6. Iodine

With regard to uncertainty and variability of biokinetics and radiation dose, ^{131}I appears to be the most frequently studied radionuclide (Dunning and Schwartz, 1981; Killough and Eckerman, 1986; Ng et al., 1990; Eckerman et al., 1999; Hamby and Benke, 1999; Harrison et al., 2001; Harvey et al., 2003; Apostoaei and Miller, 2004). In several cases parameter uncertainty analysis has been used to assess uncertainties or "imprecision" in thyroid dose from ingestion of ^{131}I (Dunning and Schwartz, 1981; Killough and Eckerman, 1986; Ng et al., 1990; Hamby and Benke, 1999; Harvey et al., 2003; Apostoaei and Miller, 2004). Conclusions vary somewhat with the age group(s) addressed and the treatment of correlation of parameter values but typically indicate that central estimates are reasonably well established despite a high inter-subject variability. For example, Harvey et al. (2003) determined lognormal "uncertainty distributions" for ^{131}I dose coefficients, with geometric standard deviation (GSD) varying from 1.55 to 2.61, depending on age and gender. Apostoaei and Miller (2004) also derived lognormal distributions but concluded that the thyroid dose coefficient is well characterized by a GSD of 1.7 for both sexes and all ages other than infants for whom the GSD is 1.8. Harvey and coworkers identified thyroid mass and the thyroid uptake fraction as the most important parameters. Apostoaei and Miller concluded that the largest contribution to uncertainty comes from thyroid mass. The existing studies provide a useful starting place for assessment of uncertainties in ^{131}I dose coefficients but must be closely examined with regard to implicit assumptions, subtle problems associated with model structure, and the extent to which the relative merits of different data sets have been addressed.

3.2.7. Iridium

No uncertainty or variability studies were found.

3.2.8. Plutonium

Several studies have addressed uncertainties in some aspects of the biological behavior or dosimetry of inhaled, ingested, or absorbed plutonium (NRC-CEC, 1997; Leggett et al., 1998; Eckerman et al., 1999; Harrison et al., 2001; Suzuki et al., 2002; Farfan et al., 2003; Aden and Scott, 2003; Leggett, 2003). For example, Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of plutonium from the gastrointestinal tract are 10^{-4} to 10^{-3} for adults or age 10 y and 10^{-4} to 10^{-2} for infants. In a series of papers, Bolch and coworkers (Bolch et al., 2001; Bolch et al., 2003; Farfan et al., 2003; Huston et al., 2003) investigated the sensitivity of predictions of ICRP's current respiratory model to uncertainties and variability in parameter values, with applications to uncertainties in lung dose from inhalation of $^{239}PuO_2$ (and ^{238}U compounds). Conclusions regarding the level of uncertainty in lung dose from inhaled $^{239}PuO_2$ varied markedly with particle size, with the GSD of the uncertainty distribution approaching 4.5 for large particles (Farfan et al.,

2003). Aden and Scott (2003) carried out a broadly similar assessment of the variability and uncertainty associated with inhaled PuO_2 for a hypothetical population of nuclear workers engaged in light work-related exercise; their conclusions are difficult to interpret in terms of uncertainty in lung dose. Suzuki et al. (2002) assessed the sensitivity of dose estimates for internally deposited ^{239}Pu to variation in the parameter values of the systemic biokinetic model for Pu recommended in ICRP Publication 67 (1993); they concluded that dose estimates were not strongly sensitive to uncertainties in parameter values. A recent retrospective examination of errors in the systemic biokinetic models for plutonium recommended over the years by the ICRP (essentially, an extensive matching of history in view of recent advances in the database) indicates that the ICRP's recent systemic biokinetic models for plutonium have been reasonably accurate predictors of cumulative activity in liver and skeleton (Leggett, 2003).

3.2.9. Polonium

No useful uncertainty or variability studies were found.

3.2.10. Radium

Uncertainties in some aspects of radium biokinetics and dosimetry have been addressed in the literature. Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of radium from the gastrointestinal tract are 0.05-0.3 for adults, 0.05-0.4 for age 10 y, and 0.08-0.8 for infants. On the basis of a literature review and limited sensitivity analysis, Leggett et al. (1998) concluded that the ICRP's systemic biokinetic model for radium has moderate to high reliability (potential factor-of-3 errors) with regard to predicted cumulative activity of ^{226}Ra in bone volume. Sensitivity analyses performed during the development of Federal Guidance Report No. 13 (Eckerman et al., 1999) suggest that dose from inhalation or ingestion of ^{226}Ra can be determined with moderately high confidence and that high confidence can be placed in external dose coefficients for important gamma emitters in the ^{226}Ra chain.

3.2.11. Ruthenium

Uncertainty studies for ruthenium focus on ^{106}Ru and are similar to studies described earlier for ^{60}Co. Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of ruthenium from the gastrointestinal tract are 0.005-0.1 for adults, 0.005-0.15 for age 10 y, and 0.005-0.2 for infants. On the basis of a literature review and limited sensitivity analysis, Leggett et al. (1998) concluded that the ICRP's systemic biokinetic model for ruthenium has low reliability (potentially order-of-magnitude error) with regard to predicted cumulative activity of ^{106}Ru in the total body. Apostoaei et al. (1998) used parameter uncertainty analysis to assess uncertainties in dose coefficients for ingestion of ^{106}Ru on the basis of a simplistic model structure and derived uncertainty factors (ratio of 97.5th to 50th percentiles of the probability distribution) of about 3 for the intestines, 6 for stomach, and 9 for other tissues. Sensitivity analyses performed during the development of Federal Guidance Report No. 13 (Eckerman et al., 1999) suggest that dose from inhalation or

ingestion of ^{106}Ru cannot be determined with much confidence and that moderately high confidence can be placed in external dose coefficients for ^{106}Ru.

3.2.12. Strontium

Uncertainties in various aspects of the biokinetics or dosimetry of ^{90}Sr have been addressed in previous studies (NRC-CEC, 1997; Bogen et al., 1997; Leggett et al., 1998; Eckerman et al., 1999; Harrison et al., 2001; Apostoaei, 2002; Apostoaei and Miller, 2004). The collective reviews and analyses indicate that fractional absorption of strontium from the gastrointestinal tract and its subsequent systemic biokinetics are reasonably well understood and that uncertainties in dose coefficients for bone surfaces and red bone marrow from ingested ^{90}Sr are relatively low. For example, Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of strontium from the gastrointestinal tract are relatively narrow (i.e., have a relatively low ratio of upper to lower estimates) compared with other incompletely absorbed elements: 0.1-0.4 for adults, 0.1-0.5 for age 10 y, and 0.15-0.75 for infants. On the basis of a literature review and limited sensitivity analysis, Leggett et al. (1998) concluded that the ICRP's systemic biokinetic model for strontium has moderate to high reliability (potential factor-of-3 error) uncertainty with regard to predicted cumulative activity of ^{90}Sr in bone volume. On the basis of an analysis of reported data, Apostoaei (2002) concluded that uncertainty in the gastrointestinal absorption fraction for strontium in adults is well represented by a lognormal distribution with GSD of 1.44 (95% confidence interval is 0.109 to 0.456). On the basis of a parameter uncertainty analysis, Apostoaei and Miller (2004) concluded that the uncertainties in ^{90}Sr ingestion dose coefficients for bone surface and red bone marrow can be represented by lognormal distributions with GSD of 2.6 and 2.4, respectively.

3.2.13. Thorium

Sensitivity analyses performed during the development of Federal Guidance Report No. 13 (Eckerman et al., 1999) suggest that dose from ingestion or inhalation of ^{232}Th cannot be estimated with much confidence, due largely to uncertainties in the fate of chain members produced in the body. On the other hand, uncertainties in external dose coefficients for important gamma emitters in the ^{232}Th chain were judged to be relatively small.

3.2.14. Uranium

Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of uranium from the gastrointestinal tract are 0.006-0.03 for adults, 0.008-0.05 for age 10 y, and 0.01-0.07 for infants. Sensitivity analyses performed during the development of Federal Guidance Report No. 13 (Eckerman et al., 1999) suggest that dose from inhalation or ingestion of ^{234}U can be determined with moderately high confidence and that high confidence can be placed in external dose coefficients for important gamma emitters in the ^{234}U chain. In a series of papers, Bolch and coworkers (Bolch et al., 2001; Bolch et al., 2003; Farfan et al., 2003; Huston et al.,

2003) investigated the sensitivity of predictions of ICRP's current respiratory model to uncertainties and variability in parameter values, with applications to uncertainties in lung dose from inhalation of $^{238}UO_2$ or $^{238}U_3O_8$ ($^{239}PuO_2$ was also addressed). Conclusions regarding the level of uncertainty in lung dose from inhaled ^{238}U oxide varied markedly with particle size, with the GSD of the uncertainty distribution approaching 5 for large particles (Farfan et al., 2003).

3.2.15. Zirconium

Harrison et al. (2001) concluded from a literature review that high-confidence intervals for average fractional absorption of zirconium from the gastrointestinal tract are 0.0001-0.01 for adults, 0.0001-0.02 for age 10 y, and 0.0001-0.04 for infants. On the basis of a literature review and limited sensitivity analysis, Leggett et al. (1998) concluded that the ICRP's systemic biokinetic model for zirconium has low reliability (potentially order-of-magnitude error) with regard to predicted cumulative activity of ^{95}Zr in bone.

3.3. SUMMARY AND CONCLUSIONS

The purpose of this project is to determine the feasibility of a comprehensive characterization of uncertainties in radiation dose coefficients and variability of dose per unit exposure. A critical task in this study (Task 3 in the Scope of Work) is to assess the quality and completeness of primary biokinetic and dosimetric data available to estimate dose from exposure to key radionuclides and identify available resources for characterizing uncertainty and variability in dose per unit intake. This report summarizes assessments performed for isotopes of selected elements. The elements H, Co, Sr, Zr, Ru, Sb, I, Cs, Ra, U, and Pu were selected for review because a large portion of the published assessments of uncertainty or variability in dose estimates address isotopes of these elements. Four other elements, C, Ir, Po, and Th, were included to illustrate the much larger class of radionuclides that has received little or no attention in this regard. Thus, the assessments are skewed toward the more frequently studied cases and should not be interpreted as indicating that uncertainty or variability in dose has been extensively studied for radionuclides in general.

To assess the quality of the data underlying current radiation dose coefficients, it is convenient to divide the data into two main categories: biokinetic data used to model the behavior of radionuclides in the human body, and dosimetric data used to model radiation transport and deposition of ionizing energy in tissues. Dosimetric data can be further divided into nuclear decay data, anthropomorphic information, and information on the relative biological effectiveness (RBE) of different types of radiation.

The confidence that can be placed in predictions of a biokinetic model depends on the quality of the underlying biokinetic data. As illustrated in Section 2, the quality of data available to model the biokinetics of radionuclides in the human body varies considerably from one element to another. One end of the spectrum is illustrated by cesium or strontium, whose biokinetics in man can be predicted with reasonably high confidence on

the basis of extensive cesium- or strontium-specific data for human subjects supplemented with information from animal studies. The other end of the spectrum is illustrated by antimony or iridium, whose biokinetics in man cannot be predicted with much confidence because the relevant databases are limited and consist almost entirely of data for laboratory animals.

Nuclear decay data represent a combination of direct measurements and application of principles of physics and have been developed in a reasonably uniform manner by researchers worldwide. Decay data for most radionuclides do not appear to represent a major source of uncertainty in dose coefficients, but sizable errors in half-lives as well as energies and yields of emissions have been identified in recent years for several radionuclides. Moreover, a number of radionuclides of potential importance in occupational, medical, or environmental settings are not addressed in any of the current databases. Surrogate nuclear decay data can be applied to radionuclides with missing decay data, but sensitivity analyses indicate that this could sometimes result in sizable errors in dose estimates.

The two main types of anthropomorphic phantoms currently in use in radiation protection are mathematical phantoms, with organs represented by regular three-dimensional shapes; and voxel phantoms, based on computed tomographic data for a real person, with each organ, tissue, or fluid represented as a set of points describing its volume and position as determined in the scan. Voxel phantoms are more realistic representations of the human body but do not have sufficient resolution to address some small target tissues in the body, particularly in the lungs and skeleton, that can be addressed using mathematical phantoms. The limitations associated with either mathematical or voxel phantoms usually do not contribute much to the total uncertainty in dose coefficients, either for internal or external exposure, but these limitations can become the dominant source of error in dose estimates involving low-energy photons or beta- or alpha-irradiation of narrow target regions from nearby tissues.

Radiobiological data indicate that alpha particles and neutrons have a larger relative biological effectiveness (RBE) than an equal absorbed dose of low-LET radiation. Ranges of estimated RBEs for alpha particles or neutrons are wide and may depend on the biological system, the observed endpoint, the dose level, the energy level, and the tissue or cancer type. Overall, experimental data for solid tumor induction with alpha particles and fission neutrons suggest a central value of about 10-30 and a range of roughly 5 to 60 for the RBE relative to low-LET radiation.

As discussed in Section 3, a number of assessments of uncertainty or variability in the biokinetics or dosimetry of radionuclides have already been published in the literature. The studies summarized in Section 3 represent the major studies but not all of the relevant literature on this topic. If a more comprehensive assessment is to be done, a more complete review of the literature should be performed at an early stage of the larger project.

The existing uncertainty assessments provide a useful starting place for characterization of uncertainties in dose coefficients for at least the following radionuclides: ^{3}H (as tritiated water) ^{14}C (as carbon dioxide or bicarbonate), ^{60}Co, ^{90}Sr, ^{95}Zr, ^{106}Ru, ^{125}Sb, ^{131}I, ^{137}Cs, ^{226}Ra, ^{234}U, and ^{239}Pu. The existing studies must be critically examined, however, with regard to implicit assumptions, subtle problems associated with model structure, and the extent to which the relative merits of different data sets have been addressed. Also, the concepts of "uncertainty" and "variability" have not been clearly distinguished in most of the published studies, and it will be necessary to review the methods and data sets used in those studies to determine which of these concepts is more nearly represented in each case.

It is not anticipated that the present project will lead to radically different methods for assessing uncertainty or variability in dose estimates. The plan is to improve existing approaches and build on existing uncertainty studies for those radionuclides that have previously been addressed, and to develop uncertainty assessments from the ground up for the many important radionuclides that have not been addressed in the literature in the context of uncertainty or variability of dose. The investigators will take into account that the most appropriate method of uncertainty analysis depends on the problem addressed, in contrast to the one-approach-fits-all view of uncertainty analysis held by some proponents of parameter uncertainty analysis (PUA). Methods that will be considered for use in each case include PUA, matching of history, and model-independent evaluations, i.e., assessment of the data represented by a model, rather than direct assessment of the model. In cases where a PUA-type analysis appears to be an appropriate approach, the analysis will take into account two critical factors that are usually missing from PUAs: the contribution of model formulation to the conclusions of the analysis, and the relative merits of different types of data.

The technical basis for developing regulations and guidance involving radiation protection includes the application of generic or reference models for dosimetry. The investigators in this project have developed a number of biokinetic and dosimetric models used internationally for radiation protection purposes and interpretation of bioassay. It is expected that their development of improved databases and assessments of uncertainties in dose estimates will result in improvements in portions of the current system of models and bolster confidence in other portions, thus improving the defensibility of the underlying technical basis.

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