Quality Management Plan

Dose Coefficient Uncertainty and Human Variation Quantification Feasibility Study

Prepared by

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1 INTRODUCTION

This Quality Management Plan (QMP) was prepared by Oak Ridge National Laboratory (ORNL) for the NRC project entitled "Dose coefficient uncertainty and human variation quantification feasibility study". In this project, ORNL is responsible for demonstrating the feasibility of a larger project to evaluate the uncertainties in current radiation dose coefficients and variability of dose per unit exposure in human populations. The project will assess the strengths and weaknesses of the primary data used as inputs to biokinetic models; variability in biokinetics and dose among humans; uncertainties and limitations associated with the structure of the models, including the ability of the models to predict biometric data such as the rate of excretion of radionuclides or effective treatments for removing radionuclides from the body; and the robustness of the models in terms of their sensitivity to uncertainties in the underlying data and biological variability.

The work is divided into two phases:

- Phase I – For selected radionuclides and intake modes, evaluation of the information underlying existing dose coefficients, the technical soundness of the coefficients, and the variability of dose per unit exposure in the population.

- Phase II – Demonstration of application of existing data and resources to quantify uncertainty in selected dose coefficients and the feasibility of expanding the analysis to a more comprehensive set of dose coefficients.

The primary objective of the QMP is to enable independent review of the work with the design objectives of transparency, traceability, accuracy, organization, archival protection of work-in-progress, and archival of technical work and deliverables.

- **Transparency.** Mathematical formulations and rationales for assumptions and parameter selections will be explicit and complete.

- **Traceability**. Citations of references will be sufficiently complete to enable independent retrieval of copies of cited material.

- **Accuracy**. Results of calculations will be checked thoroughly for accuracy and consistency with the design objectives.

- **Organization**. Records will be logically organized and indexed to facilitate data retrieval.

- **Archives**. Sufficient backup of files and work in progress will be maintained to guard against loss due to unexpected events, including computer malfunction, fire, or theft.

The QMP is intended to be a current statement of ORNL's approach to implementing the elements of this contract. The QMP may be revised and updated as the project progresses. Any

revisions shall be submitted to the NRC as an attachment to the following monthly status letter report. The QMP and subordinate documents shall be maintained as controlled documents.

Section 2 discusses the quality requirements and responsibilities. Section 3 addresses the preparation and review of technical information. Section 4 discusses document preparation. An illustration of the format (database) of fundamental information required for this project is provided in Appendix A.

2 QUALITY REQUIREMENTS AND RESPONSIBILITIES

2.1 General Requirements

The basic quality requirements imposed on this project are:

- The technical basis for all input data and parameters shall be documented in sufficient detail to permit independent verification and reviews and facilitate audit of project results.

- Documents and references necessary to establish the technical basis shall be maintained and organized in a secure location at the investigators' work site.

- Technical changes must be documented and traceable.

- Each investigator shall be responsible for saving and backing up his work at appropriate intervals. He shall maintain an automatically updated anti-virus program, such as McAffee Virus Scan or Norton Anti-Virus, on his computer.

- Backups shall be saved on CDs and maintained in a secure location separate from the primary work site. It shall be the responsibility of the staff member to ensure that no more than one week's work would be at risk under any foreseeable circumstances.

2.2 Software Requirements

Software developed by this project shall be verified and validated (V&V). The following basic quality requirements shall be imposed on project-developed software:

- Verification of source code:
  - Is the source code understandable?
  - Are all variables properly specified and used?
  - Is there satisfactory error checking?

- Verification of program integration:
  - Does the program interface properly with external files?
  - Are all elements of the integrated program properly identified?

· Verification of test results:
  - Have all test cases been executed correctly?
  - Do the results agree with expected answers?

2.3 Responsibilities

The project will be carried out by two investigators. The ORNL Project Manager (PM) is Keith Eckerman and the principal analyst (PA) is Rich Leggett. The responsibilities of the investigators regarding implementation of the various aspects of this QMP are described below.

The PM will be ultimately responsible for ensuring that elements of this QMP are carried out and will provide QA on material prepared by the PA. The PM will be directly involved in some project tasks, particularly those involving nuclear decay data, radiation transport models, and development of computer codes.

The PA will collect, analyze, and reduce the biokinetic data used in the project; develop and maintain the biokinetic database; serve as main author of reports and manuscripts; and assure that the data and mathematical formulae are accurate, complete, verifiable, properly documented, and correctly encoded as computer models.

3 PREPARATION AND REVIEW OF TECHNICAL INFORMATION

3.1 Dosimetric Databases

3.1.1 Background

A key task in this project is assessment of information underlying dose coefficients for selected exposures to radionuclides. That information may be divided into two categories:

- biokinetic data used to model the behavior of radionuclides in the human body
- nuclear decay data used to model radiation transport and deposition of ionizing energy in tissues

Biokinetic data are required for assessment of internal exposure, while nuclear decay data are required for assessment of both internal and external exposure.

Current dose coefficients for radionuclides are point estimates based on biokinetic models developed from the biokinetic data, together with activity-to-dose conversion models developed from the nuclear decay data. These models are intended to represent typical members of the exposed population or specific subgroups of the population such as adults or infants.

Basic nuclear decay data for radionuclides have been developed in a reasonably uniform manner by researchers worldwide and represent a combination of direct measurements and application of sound principles of physics. Reasonably detailed biokinetic data exist for some radionuclides, but biokinetic information as a whole is much less complete and much less uniformly derived than

nuclear decay data. As a rule (with exceptions to be addressed in this project), the biokinetics of radionuclides represents the dominant source of uncertainty in radiation dose coefficients for internally deposited radionuclides and the dominant source of variability of radiation doses in the population.

3.1.2 Nuclear decay databases used in this project

Extensive tabulations of nuclear decay data are available. Two main nuclear decay databases, referred to as the ICRP 38 (ICRP Publication 38, 1983) and JAERI (Japan Atomic Energy Research Institute) databases, will be used in this project. The ICRP 38 database, which contains nuclear decay data for over 800 radionuclides, was used in the derivation of current dose coefficients for internal and external exposure to radionuclides. The JAERI database, developed recently in a joint project by JAERI and ORNL (Endo et al., 2003), updates decay data given in the ICRP 38 database and provides data for additional radionuclides.

The JAERI database represents best current information on radiation emissions from decay of radionuclides and will used in this project as baseline nuclear decay data, although the sources and extent of uncertainties in these data will be critically assessed. The ICRP 38 database will be used only as required in assessments of potential errors in current dose coefficients.

3.1.3 Development of a biokinetic database

There exists no biokinetic database analogous to the ICRP 38 or JAERI databases for nuclear decay data. Biokinetic information needed for this feasibility study will be collected and organized within a "starter" biokinetic database. This database will be accessible to the NRC Project Officer and reviewers through a website and will be key to the transparency, traceability, accuracy, and organization of much of the technical work and deliverables in this project. The biokinetic database, together with the JAERI database of nuclear decay data, will represent the primary input for computer calculations and, along with computer results, will form the basis for the manuscripts produced in this project.

In contrast to nuclear decay data, biokinetic data for a radionuclide generally are not sufficiently homogeneous to allow reduction to a uniform tabulation of numerical values. Biokinetic data have been derived and reported in a variety of forms, all of which may be required to describe the current level of understanding of the biokinetics of a radionuclide. 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. The goal is to preserve a flexible format while achieving efficiency and sufficient organization that the database can be readily understood and applied by those not involved in its preparation.

The database will be constructed with these main goals in mind:

- The database should be self-contained, that is, all data should be transparent and traceable from information contained within the database.

- Individual numerical data sets representing studies of a specific biokinetic property of a substance should be exportable to spreadsheets, computer input files, graphics packages, and tables within manuscripts.
- The file should include qualitative information in the form of brief comments needed to interpret the data and/or relate it to physiological processes.

The database for a substance with distinctive biokinetic properties (e.g., an element, or a specific compound of an element that behaves differently from other compounds) will consist of a single Microsoft Word file. The format will represent a compromise between a spreadsheet and a report. The file will consist of a collection of individual data sets in table format, which will allow their export to spreadsheets or computer input files; for example, any rectangular portion of a Word table may blocked, copied, and pasted into a standard spreadsheet. An individual data set within the database for a substance will represent uniformly derived biokinetic information and will typically come from a single study of a specific biokinetic property of that substance or physiologically related substances. Short text identified as "Comment" will be placed before or after individual data sets as explanation of the nature of the data.

Within the database for a substance, biokinetic data will be divided into five main categories (Leggett, 2001):

- 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
- Other (any biokinetic information other than H1, H2, A1, or A2 data, e.g., *in vitro* data)

Included under each of these main headings may be any number of separate data sets. More than one data set may come from the same source, e.g., fractional absorption of an element from the gastrointestinal tract may represent one data set, and time-dependent urinary excretion of the radionuclide as determined in the same study may represent a separate data set. A graphical representation of all or part of a data set may be included as an aid in understanding the data. The full reference to the data set will be included in a reference list at the end of the file.

The completeness of the database for a substance will depend on the intended applications of that portion of the database in this feasibility study. In some applications it will be necessary to collect a reasonably complete set of accessible information on the biokinetics of a radionuclide. In other cases, particularly in assessments of variability in the population, it will suffice to collect information on a particular aspect of the biokinetics of a radionuclide (e.g., fractional absorption from the gastrointestinal tract, or the rate of excretion in urine). In any case, the biokinetic database developed in this project for a given radionuclide will provide a starting place for development of a more comprehensive database to be used in a larger project on uncertainties and variability in radiation doses.

A biokinetic database is illustrated in Appendix A for carbon reaching blood as CO_2 (e.g., inhaled CO_2 is absorbed to blood in this form). In this case, H2 and A2 data (i.e., human and animal data on chemical or physiological analogies) include data for certain other carbon compounds, such as bicarbonate, for which the carbon label becomes largely incorporated in the same physiological pathways as the carbon label of CO_2.

A website will be established for archival and retrieval of the biokinetic database, as well as other products of this project such as draft reports. The password-protected site will be accessible by the NRC Project Officer, his designees, and project reviewers. A database file can be downloaded, and formatted data from the file can be exported by the user. This will facilitate reviews and quality checks on the results of the project.

Names of archived files will include dates. All generations of files will be maintained on the PA's PC and also on CD backups. Only the latest version of a file will be available on the website.

3.2 Preparation of Deliverables

Deliverables will be prepared by the PA and reviewed by the PM. Each deliverable will be revised on the basis of the PM's review before submission to the NRC Project Officer and/or external reviewers.

Deliverables will be sufficiently detailed that a technically qualified person can understand and trace the information used, review and reproduce the analysis, determine whether the assumptions are reasonable, and verify the results without consulting the originator. Systematic checks and comparisons will be performed independently by the two investigators to ensure the accuracy of calculations. Each deliverable will include a list of all articles, reports, or books used to develop the analyses. The format of references will be that currently used by the journal Radiation Protection Dosimetry.

Two of the deliverables will be in the form of manuscripts ready for submission to the peer-reviewed open literature. It is expected that these manuscripts will be submitted to Radiation Protection Dosimetry, although an alternate journal such as Health Physics may be selected if agreed by the NRC Project Officer and investigators. Transparency, traceability, reproducibility, and accuracy of information contained in manuscripts submitted to these scientific journals are assessed by at least two experts in the field, with anonymity of experts helping to assure a properly critical assessment.

The intent is to preserve a flexible format in the preparation of manuscripts that does not hinder performance and the preparation of deliverables while maintaining the required level of quality control and assurance. As a minimum, each manuscript will include: a concise statement of the problem and the purpose of the work; the rationale for the selection and verification of parameter values and citation of the source documents; the rationale for all assumptions made in the analyses; model and scenario descriptions; descriptions of the method of solution; and explicit mathematical formulations, numerical calculations, and derivations of any equations not in common usage; and a summary of results including tables, charts, graphs, or any other type of presentation of results that the investigators and NRC Project Officer judge to be appropriate.

For each deliverable, a corresponding review document will be maintained on the website. The website will be designed so that reviewers can access the document and enter their comments directly into the review document. In this way, the review file will include all review comments received and their resolution, as added to the website document by the PA or PM.

3.3 Control and Management of Software

3.3.1 Software developed for this project

The biokinetic database described earlier will be a primary software tool for analyses and calculations in this project. Individual data sets within the larger database will be formatted to allow export to a computer-readable file or spreadsheet. Spreadsheets used in this project will be developed on the PC-based platform running proprietary, commercial software, typically Microsoft Excel®.

Dose computations will be performed using the DCAL (DOSE CALCULATION) software developed at ORNL and extensions of that code that will be developed within this project to perform uncertainty and sensitivity analyses. DCAL is a comprehensive biokinetics, dosimetry, and risk computational system designed to serve current needs in radiation dosimetry and risk analysis. It performs biokinetic and dosimetric calculations for acute intake of a radionuclide by inhalation, ingestion, or injection into blood. DCAL has been extensively tested and has been compared with several widely used solvers for biokinetic models and systems of differential equations. Checks of the DCAL solver against independent codes with much different solvers have been published (Leggett et al., 1993). DCAL was used by a task group of the ICRP to derive or check the dose coefficients given in its series of documents on age-specific doses to members of the public from intake of radionuclides (ICRP, 1989, 1993, 1994, 1995a, 1995b); numerous comparisons were made between DCAL and three independently derived codes used by radiation protection agencies in other countries. DCAL was used to derive all radiation risk coefficients given in Federal Guidance Report No. 13 (Eckerman et al., 1999). Extensions of DCAL to be developed in this project will receive rigorous quality assurance similar to that already applied to the basic DCAL code, including numerous checks against independent methods of calculation.

3.3.2 Commercial software

Commercial computer programs intended for use in this project are described below. This listing does not include non-technical programs such as word processing or project management software.

Crystal Ball Version 5.1 (2000). Crystal Ball, a forecasting and risk analysis program, is used as an add-on to Microsoft Excel. It uses Monte Carlo sampling methods to calculate a distribution of results and will perform a statistical analysis of these results, producing such metrics as the mean, median, and 95th percentile. Crystal Ball will sample from an assumption cell in the Excel worksheet that contains a probability distribution defined by the user and calculate a range of possible outcomes in the forecast cell, as well as the likelihood of achieving each of them. The Monte Carlo method, as used by Crystal Ball, is accomplished with three simple steps which are repeated for a set number of times defined by the user. These steps are (1) generating random numbers for assumption cells, (2) calculating the entire spreadsheet, and (3) displaying results in a forecast chart. This program is used as an uncertainty analysis tool.

Sandia National Laboratory LHS Software (1998). Sandia National Laboratory's Latin Hypercube Sampling (LHS) software has been used extensively in probabilistic risk assessment (PRA) during the past fifteen years. In 1998 the software was upgraded extensively and made available for Windows operating systems. Although Crystal Ball includes LHS capabilities, Sandia package (Wyss and Jorgensen, 1998) has the advantage of being readily integrated into production-type codes.

Compac Visual Fortran (2001). Compac Visual Fortran, formerly DIGITAL Fortran, is a set of software tools for developing 32-bit Fortran applications. It includes Fortran 95, Fortran 90, and High Performance Fortran language features. The toolset includes a compiler, editor, linker, debugger, profiler, video graphics and user interface library, and C- and assembly-language interfaces.

MCNP 5.0 (2003). MCNP is a general-purpose, continuous-energy, generalized geometry, time-dependent, coupled neutron-photon-electron Monte Carlo transport code system. MCNP treats an arbitrary three-dimensional configuration of materials in geometric cells bounded by first- and second-degree surfaces and some special fourth-degree surfaces. Pointwise continuous-energy cross section data are used, although multigroup data may also be used. Fixed-source adjoint calculations may be made with the multigroup data option. For neutrons, all reactions in a particular cross-section evaluation are accounted for. Both free gas and *S(alpha, beta)* thermal treatments are used. Criticality sources as well as fixed and surface sources are available. For photons, the code takes account of incoherent and coherent scattering with and without electron binding effects, the possibility of fluorescent emission following photoelectric absorption and absorption in pair production with local emission of annihilation radiation. A general source and tally structure is available. The tallies have extensive statistical analysis of convergence. Rapid convergence is enabled by a wide variety of variance reduction methods.

PowerBASIC Console Compiler (2002). The PowerBASIC Console Compiler for Windows creates executables (.EXE files) capable of running in the Win32 environment (ME, Windows NT, 2000, and XP). PowerBASIC typically is used in the development of various utility modules for processing data or data visualization, and in the development of numerical algorithms. Many of the utility modules within DCAL were developed for this compiler. Alternative numerical methods have been implemented with this compiler to validate and verify calculations in the production codes. Depending on the application, additional capabilities may be provided by PowerBASIC libraries for the compiler to enhance graphic and database activities.

If additional programs are needed, the program's documentation will be relied upon to demonstrate that the program in question performs the desired calculation. Once the PM has been convinced that a new program performs as asserted, that program can be added to the list of approved software in a revised Project Quality Management Plan. Software can also be added to the list at the direction of the NRC Project Officer.

Non-technical software, such as word processing or project management software, does not have to be approved prior to its use in the project.

3.4 Verification and Validation (V&V)

Verification asks the question: Was the proposed solution correctly implemented? *Validation* asks the question: Will the proposed solution correctly solve the problem?

In the present project, *verification* refers primarily to solving models, implementing computer codes, verifying input data, and confirming the accuracy and completeness of documentation. With regard to the model solver and implementation of compute codes, the verification process is addressed in Section 3.3.1 in connection with the DCAL code; that code will be used to solve all models and will form the core of new software developed in this project. Input data taken from the biokinetic and dosimetric databases will be systematically re-checked against original sources. Documentation will be checked independently by the PA and PM for completeness as well as transparency of descriptions of models, assumptions, algorithms, and computations.

Project tools and results requiring *validation* include individual dosimetric models (biokinetic models or activity-to-dose conversion models) as well as the overall methods for assessing uncertainty and variability of dose.

- Validation of individual dosimetric models refers to a characterization of the expected level of accuracy of these models, as opposed to demonstration that the models are accurate.
- Validation of the overall methods refers to demonstration that these methods meet the goals of this project, that is, that they result in reproducible and meaningful characterizations of uncertainty in dose coefficients and variability of dose in the population.

Many of the dosimetric models currently used in radiation protection can be tested against independent observations, including data developed since the models were developed or previously available data that were not considered in model development. It must be considered that observations as well as model predictions may involve important uncertainties and that the independent observations should be critically assessed before this type of model validation if performed:

- Are the observations representative of the population of interest?
- Are the observations relevant to exposure conditions of interest?
- Were the observations produced by reliable measurement techniques?

After elimination of questionable or potentially irrelevant observations, model predictions will be compared with remaining observations. The quality of the resulting model "validation" will be described in terms of a uniform measure of model reliability such as the "model reliability index" defined by Williams and Leggett (1984).

Whether or not model-independent observations are available, the model validation process will critically examine the following aspects of individual models addressed in this project:

- What is the logical foundation of the model structure, including the basis for extrapolating to times or situations outside the range of observations?
- For process models, how completely are the processes understood and are known processes fully and adequately represented in the model?
- Does the full model (structure together with parameter values) take account of all pertinent data?
- Were the relative merits of different data sources adequately addressed in the selection of parameter values?
- Was the selection process for model components (compartments, paths of movement, and parameter values) fully documented and adequately described in deliverables?
- How sensitive are different types of model predictions to gaps in the information, with regard either to qualitative processes or quantitative model components?

Validation of the overall methods for evaluating uncertainties and variability of doses will include critical examination of the following aspects of the methodology:

- Is variability in the population adequately described by variability in reported data? For example, is apparent variability overstated due to variability in the measurement technique or understated due to homogeneity of study groups?
- Are limitations in model structure properly reflected in the characterizations of uncertainty?
- Do the characterizations of uncertainty properly take into account the relative merits of different types and sources of data?
- Do the characterizations of uncertainty take full account of the quality, relevance, and completeness of each data type?
- Does the methodology generate reasonable descriptions of the extent to which dose estimates will differ if based on alternate but equally plausible models?

- For relatively simple test cases, do the quantitative uncertainty statements generated by the methodology agree reasonably well with expectations and, if not, why not?
- Do the characterizations of uncertainty accurately represent the logical conclusions to be drawn from the underlying definitions, postulates, and input data.

4 DOCUMENT CONTROL

The PA will maintain a hard-copy file of all calculations, references, and deliverables during the period of performance of each task, including the period for NRC comments. These will be kept in a filing cabinet in the PA's office, Room 255, Building 1060COM, Commerce Park, Oak Ridge, TN. Calculations and documents will be given to the PM for review before transmittal to the NRC Project Office. The PA will maintain a file of copies of the original and all updated versions of revised documents.

A document index will be maintained. The document index will indicate the title of each document entered, its document number (if any), the date or revision of the document, the author(s), the date entered into the filing cabinet, and its location within the cabinet. If requested, all project records will be turned over to the NRC at the end of the project. If the records are not requested by the NRC, they shall be maintained at ORNL for a period of one year after termination of the project.

5 REFERENCES

Crystal Ball Version 5.1. 2000. Decisioneering, Inc., Denver.

Compaq Visual Fortran (2001). Compaq Computer Corporation. Houston, Texas.

Eckerman, K. F.; Leggett, R. W.; Nelson, C. B.; Puskin, J. S.; Richardson, A. C. B. (1999). Cancer risk coefficients for environmental exposure to radionuclides. Federal Guidance Report No. 13, EPA 402-R-99-001.

Endo, A.; Yamaguchi, Y.; Eckerman, K. F. (2003). Development and assessment of a new radioactive decay database used for dosimetry calculation. Radiat. Prot. Dosim. 105:565-569.

International Commission on Radiological Protection (1983). Radionuclide Transformations Energy and Intensity of Emissions. ICRP Pub. 38. Oxford: Pergamon Press.

International Commission on Radiological Protection (1989). Age-Dependent Doses to Members of the Public from Intake of Radionuclides, Part 1, ICRP Pub. 56 (Pergamon Press, Oxford).

International Commission on Radiological Protection (1993). Age-Dependent Doses to Members of the Public from Intake of Radionuclides, Part 2, ICRP Pub. 67 (Pergamon Press, Oxford).

International Commission on Radiological Protection (1994). Dose Coefficients for Intakes of Radionuclides by Workers. ICRP Pub. 68 (Pergamon Press, Oxford).

International Commission on Radiological Protection (1995a). Age-Dependent Doses to Members of the Public from Intake of Radionuclides, Part 3, ICRP Pub. 67 (Pergamon Press, Oxford).

International Commission on Radiological Protection (1995b). Age-Dependent Doses to Members of the Public from Intake of Radionuclides, Part 4, ICRP Pub. 71 (Pergamon Press, Oxford).

Leggett, R. W.; Eckerman, K. F.; Williams, L. R. (1993). An elementary method for implementing complex biokinetic models, Health Physics 64:260-278.

Leggett, R. W. (2001). Reliability of the ICRP's dose coefficients for members of the public. 1. Sources of uncertainty in the biokinetic models. Radiation Protection Dosimetry 95:199-213.

MCNP 5.0 (2003). Monte Carlo N-Particle Transport Code System. Oak Ridge National Laboratory RSICC Computer Code Collection, Oak Ridge, Tenn.

PowerBASIC Console Compiler. Reference Guide (2002). PowerBASIC, Inc.

Williams, L. R.; Leggett, R. W. (1984). A measure of model reliability. Health Phys. 46, 85-95.

Wyss, G.D.; Jorgensen, K.H. (1998). A user's guide to LHS: Sandia's Latin Hypercube Sampling Software. SANDIA98-02010. Sandia National Laboratory, Albuquerque, NM.

APPENDIX A: ILLUSTRATIVE BIOKINETIC DATABASE: CARBON REACHING BLOOD AS CO_2

H1 data: Direct information – quantitative measurements of the substance of interest in human subjects

Data Set H1-1: Concentration of ^{14}C in breath in six healthy adult male humans over an 18-day period following single breath inhalation of 3.7×10^6 Bq $^{14}CO_2$.

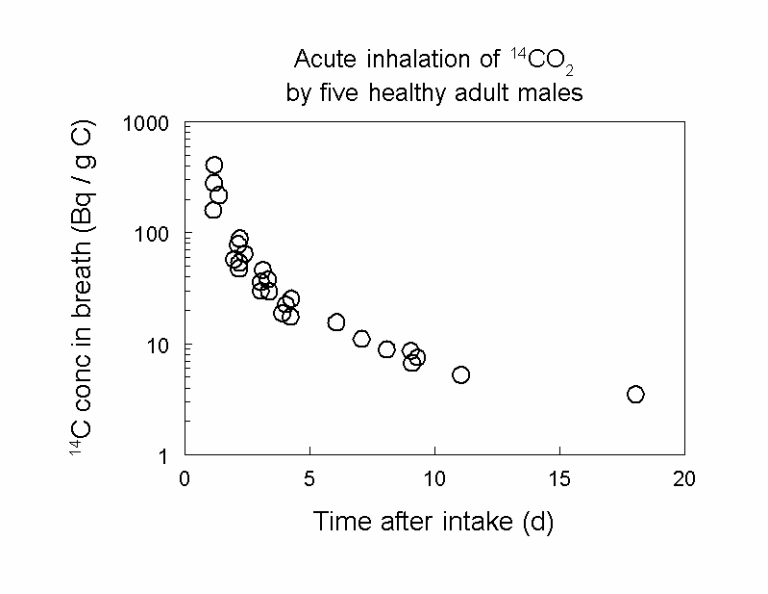
Source of H1-1: Whillans and Johnson, 1984

Comments (H1-1): Data are for individual subjects. Uncertainty in intake by each subject is +/- 20%.

Exportable data (H1-1):

Time (d)	^{14}C concentration in breath (Bq / gC)
1.155	160
1.179	279
1.196	406
1.372	217
1.993	57.5
2.143	78.1
2.189	47.4
2.194	53.7
2.216	88.3
2.406	64.3
3.052	29.9
3.060	36.0
3.139	46.0
3.335	38.0
3.392	29.5
3.915	18.8
4.060	22.6
4.252	17.5
4.269	25.4
6.083	15.5
7.088	11.0
8.098	8.86
9.049	8.61
9.106	6.70
9.315	7.54
11.067	5.23
18.054	3.50

Graphical representation (H1-1):



Comments (Graphical representation, H1-1): The concentration of ^{14}C in breath decreased by three orders of magnitude the first day (not shown).

Data Set H1-2: Concentration of ^{14}C in urine in five healthy adult male humans over an 18-day period following single breath inhalation of 3.7 x 10^6 Bq $^{14}CO_2$ (uncertainty in intake, +/-20%).

Source of H1-2: Whillans and Johnson, 1984

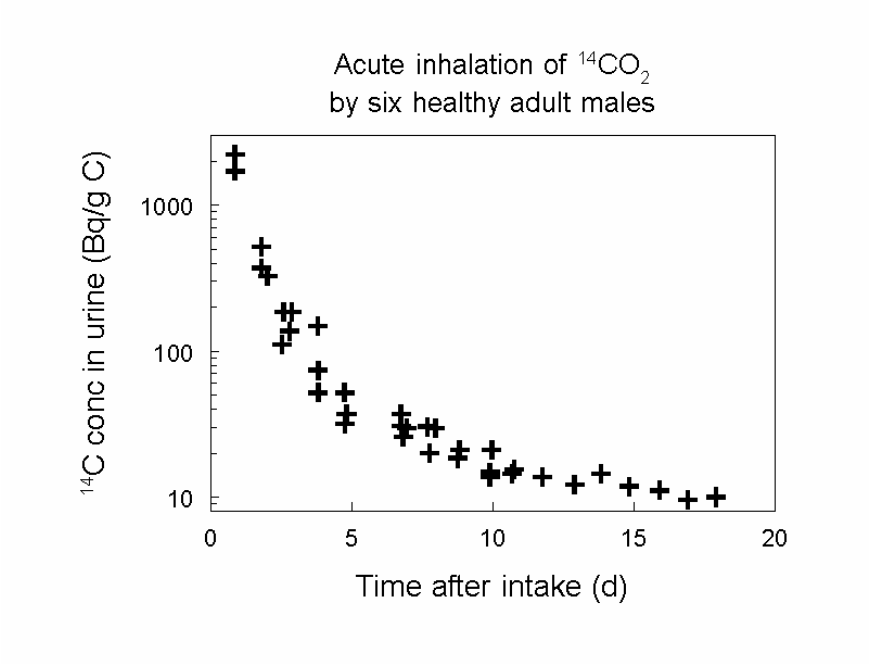
Comments (H1-2): Data are for individual subjects. Uncertainty in intake by each subject is +/-20%.

Exportable data (H1-2):

Time (d)	^{14}C concentration in urine (Bq / gC)
0.861	2220
0.862	1700
1.800	519
1.802	370
2.018	326
2.525	111
2.594	185
2.811	137
2.812	137
2.879	185
3.810	148
3.816	74.1
3.817	51.9
4.747	51.9
4.751	31.9

4.820	37.0
6.750	37.0
6.754	30.7
6.823	25.9
6.965	29.6
7.682	30.4
7.755	20.0
7.968	29.6
8.759	18.5
8.825	21.1
8.829	21.1
9.899	14.8
9.902	13.7
9.970	21.1
10.688	14.4
10.757	15.6
11.757	13.7
12.901	12.2
13.828	14.4
14.830	11.9
15.902	11.1
16.904	9.63
17.903	10.0

Graphical representation (H1-2):



H2 data: Observations of the behavior of chemically similar and/or physiologically related substances in human subjects

Data set H2-1: Recovery of ^{14}C in CO_2 expired or lost through skin during continuous subcutaneous infusion of [^{14}C]bicarbonate.

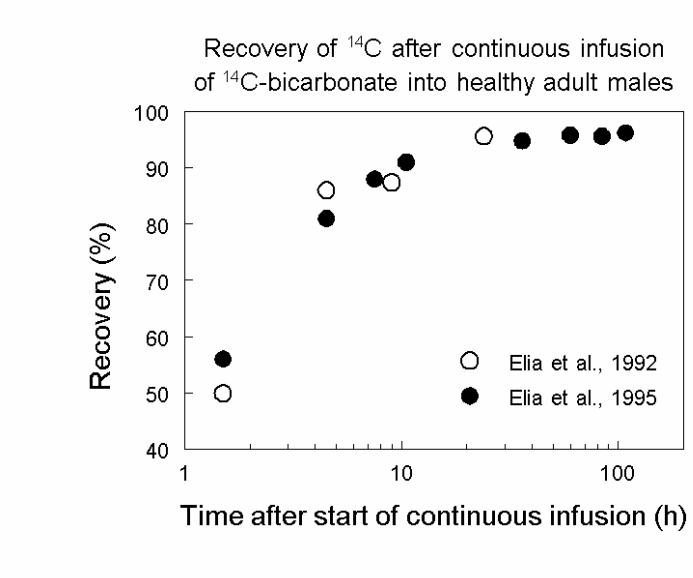
Source of H2-1: Elia et al., 1992

Comments (H2-1): Data are for six healthy subjects infused for 36 h. Average recovery of label expressed as recovery during a given period divided by the amount infused during that period. ^{14}C follows nearly the same physiological pathways whether administered as bicarbonate or carbon dioxide because the two forms are largely converted to a common form in blood.

Exportable data (H2-1):

Time since start of study (h)		Gaseous CO_2	
Start of period	End of period	Mean	SD
0	3	49.9	2.4
3	6	86.0	4.0
6	12	87.4	4.1
12	36	95.6	1.1

Graphical representation (H2-1)



Comments (Graphical representation, H2-1): Includes data from Elia et al. 1992 and Elia et al. 1995 (described below). Time = midpoint of measurement period, e.g., 1.5 h for a measurement period of 0-3 h after the start of infusion.

Data set H2-2: Recovery of ^{14}C in urine during continuous subcutaneous infusion of [^{14}C]bicarbonate.

Source of H2-2: Elia et al., 1992

Comments (H2-2): Data are for six healthy subjects infused for 36 h. Average recovery of label expressed as recovery during a given period divided by the amount infused during that period.

Exportable data (H2-2):

Time since start of study (h)		Urinary label	
Start of period	End of period	Mean	SD
0	3	0.4	0.2
3	6	0.8	0.5
6	12	1.4	0.6
12	36	1.9	0.4

Graphical representation (H2-2): None

Data Set H2-3: Recovery of ^{14}C in CO_2 expired and lost through skin during continuous subcutaneous infusion of [^{14}C]bicarbonate.

Source of H2-3: Elia et al., 1995

Comments (H2-3): Data are for five healthy adult male subjects infused for 120 h. Average recovery of label expressed as recovery during a given period divided by the amount infused during that period.

Exportable data (H2-3):

Time since start of study (h)		Gaseous CO_2	
Start of period	End of period	Mean	SD
0	3	56	20
3	6	81	8
6	9	88	5
9	12	91	4
24	48	94.8	1.6
48	72	95.8	0.9
72	96	95.6	0.7
96	120	96.2	1.3

Graphical representation: Combined with Elia et al. 1992 (above).

A1 data: Observations of the behavior of the substance of interest in non-human species

Data Set A1-1: Distribution of ^{14}C in tissues of mice during prolonged inhalation of $^{14}CO_2$.

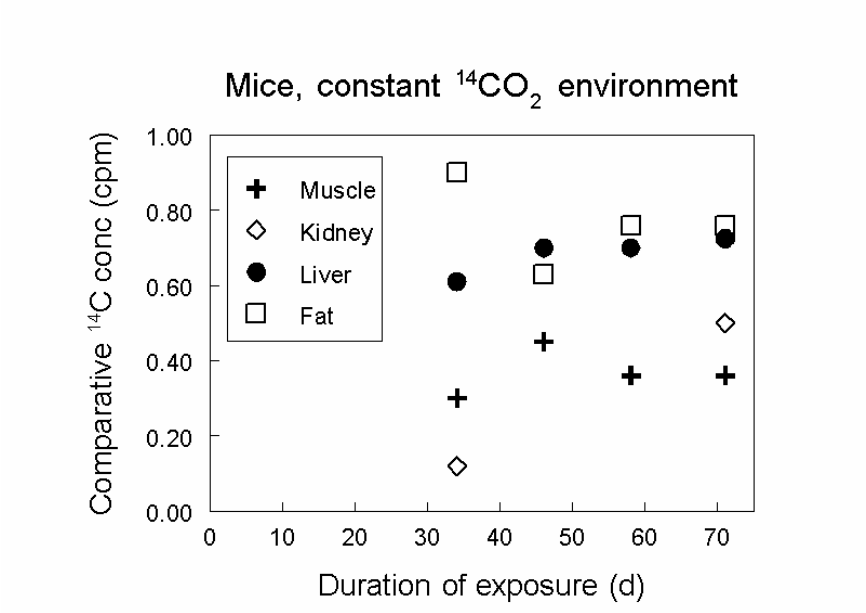
Source of A1-1: Joftes, 1967

Comment (A1-1): Data are difficult to relate to intake and hence represent only relative concentrations in different tissues. NM in table indicates not measured.

Exportable data (A1-1):

Time after start of exposure (d)	^{14}C concentration (cpm)			
	Muscle	Kidney	Liver	Fat
34	0.3	0.12	0.61	0.9
46	0.45	NM	0.7	0.63
58	0.36	NM	0.7	0.76
71	0.36	0.5	0.725	0.76

Graphical representation (A1-1):



Data Set A1-2: Removal half-times of ^{14}C from tissues of mice following 34-day exposure to $^{14}CO_2$.

Source of A1-2: Buchanan, 1951

Comment (A1-2): Two half-times were calculated for each tissue, one for 3-day period immediately after exposure and the other for 25-day period starting 20 days after exposure.

Exportable data (A1-2):

Tissue	Half-time (d)	
	0-3 d post exposure	20-45 d post exposure
Kidney	3.9	11.5
Heart	8.8	12.7
Liver	2.4	13.8
Lungs	4.4	15.0
Pancreas	4.3	17.0
Ileum	1.5	18.6
Cerebellum	7.5	19.6
Colon	2.1	23.3
Spleen	3.1	31.5
Muscle	13.5	46.0
Costal cartilage	9.0	50.0
Skin	7.1	63.0

Graphical representation: None

A2 data: Observations of the behavior of chemically similar and/or physiologically related substances in non-human species

Data Set A2-1: Retention of ^{14}C in total body and skeleton of mice following injection of [^{14}C]bicarbonate.

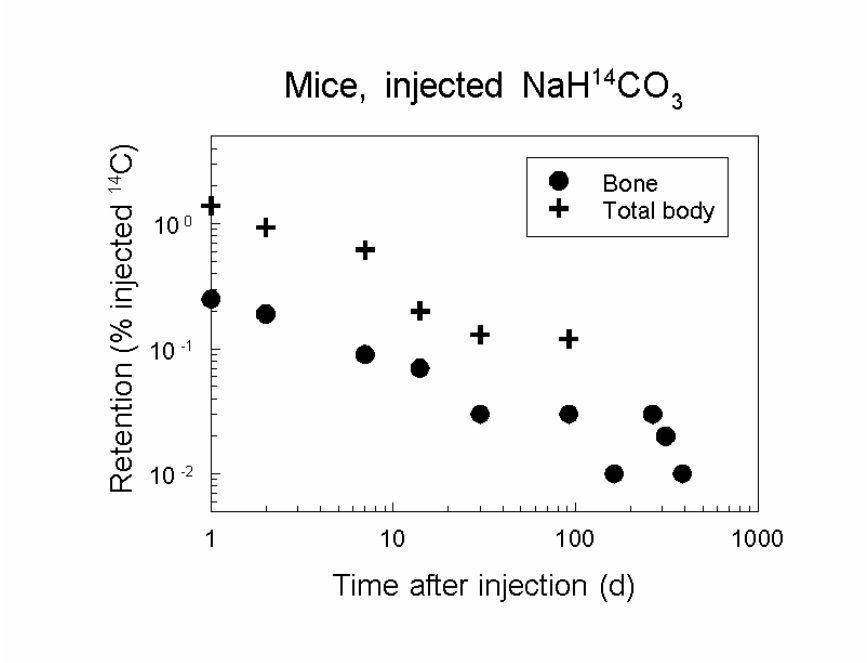
Source of A2-1: Skipper, 1952

Comment (A2-1): ^{14}C follows nearly the same physiological pathways whether administered as bicarbonate or carbon dioxide because the two forms are largely converted to a common form in blood.

Exportable data (A2-1):

Time after injection (d)	Retention (% of injected ^{14}C)	
	Total body	Skeleton
1	1.4	0.25
2	0.94	0.19
7	0.62	0.09
14	0.20	0.07
30	0.13	0.03
90	0.12	0.03
160	<0.02	0.01
265	<0.04	0.03
315	--	0.02
385	--	0.01

Graphical representation (A2-1):



REFERENCES TO APPENDIX A

Buchanan, D. L. Uptake and retention of fixed carbon in adult mice. J. Gen. Physiol. 34:737-759 (1951).

Elia, M., Fuller, N. J., and Murgatroyd, P. R. *Measurement of bicarbonate turnover in humans: applicability to estimation of energy expenditure.* Am. J. Physiol. 263, E676-E687 (1992).

Elia, M., Jones, M. G., Jennings, G., Poppitt, S. D., Fuller, N. J., Murgatroyd, P. R., and Jebb, S. A. *Estimating energy expenditure from specific activity of urine urea during lengthy subcutaneous $NaH^{14}CO_3$ infusion.* Am. J. Physiol. 269, E172-E182 (1995).

Joftes, D. L. *^{14}C content of tissues of mice after prolonged breathing of $^{14}CO_2$-contaminated air.* Radiat. Res. 31, 541-542 (1967).

Skipper, H. E. *The hazard involved in the use of carbon-14.* Nucleonics 10, 41-47 (1952).

Whillans, D. W. and Johnson, J. R. *Interpretation of urinary excretion rate data in the assessment of uptakes of carbon-14.* In: Assessment of radioactive contamination in man. Vienna: Proceedings of the International Atomic Energy Agency (IAEA), IAEA-SM-276/50, pp. 525-532 (1984).