Published in final edited form as:

Radiat Res. 2015 January ; 183(1): 27–41. doi:10.1667/RR13729.1.

The Two-Dimensional Monte Carlo: A New Methodologic Paradigm for Dose Reconstruction for Epidemiological Studies

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Abstract

Retrospective dose estimation, particularly dose reconstruction that supports epidemiological investigations of health risk, relies on various strategies that include models of physical processes and exposure conditions with detail ranging from simple to complex. Quantification of dose uncertainty is an essential component of assessments for health risk studies since, as is well understood, it is impossible to retrospectively determine the true dose for each person. To address uncertainty in dose estimation, numerical simulation tools have become commonplace and there is now an increased understanding about the needs and what is required for models used to estimate cohort doses (in the absence of direct measurement) to evaluate dose response. It now appears that for dose-response algorithms to derive the best, unbiased estimate of health risk, we need to understand the type, magnitude and interrelationships of the uncertainties of model assumptions, parameters and input data used in the associated dose estimation models. Heretofore, uncertainty analysis of dose estimates did not always properly distinguish between categories of errors, e.g., uncertainty that is specific to each subject (i.e., unshared error), and uncertainty of doses from a lack of understanding and knowledge about parameter values that are shared to varying degrees by numbers of subsets of the cohort. While mathematical propagation of errors by Monte Carlo simulation methods has been used for years to estimate the uncertainty of an individual subject's dose, it was almost always conducted without consideration of dependencies between subjects. In retrospect, these types of simple analyses are not suitable for studies with complex dose models, particularly when important input data are missing or otherwise not available. The dose estimation strategy presented here is a simulation method that corrects the previous deficiencies of analytical or simple Monte Carlo error propagation methods and is termed, due to its capability to maintain separation between shared and unshared errors, the two-dimensional Monte Carlo (2DMC) procedure. Simply put, the 2DMC method simulates alternative, possibly true, sets (or vectors) of doses for an entire cohort rather than a single set that emerges when each individual's dose is estimated independently from other subjects. Moreover, estimated doses within each simulated vector maintain proper inter-relationships such that the estimated doses for members of a cohort subgroup that share common lifestyle attributes and sources of uncertainty are properly correlated.

The 2DMC procedure simulates inter-individual variability of possibly true doses *within* each dose vector and captures the influence of uncertainty in the values of dosimetric parameters *across* multiple realizations of possibly true vectors of cohort doses. The primary characteristic of the 2DMC approach, as well as its strength, are defined by the proper separation between uncertainties shared by members of the entire cohort or members of defined cohort subsets, and uncertainties that are individual-specific and therefore unshared.

INTRODUCTION

Dose reconstruction involves the application of principles of radiation exposure and dose assessment to estimate radiation doses received by individuals from past exposure events. While dose reconstruction has several possible purposes (1), its use to support epidemiologic studies whose goal is to quantify radiation risk² is its most exacting and, we believe, important application. Over the past three or more decades, estimation of radiation doses used to support epidemiologic investigations has progressed through several stages of conceptualization and methodologic developments. Improvements in dose reconstruction methods have made it possible to more realistically estimate the true dose to members of a cohort and the strategies have evolved from simple exposure assessment equations to complex computer modeling that simulates the release, environmental transport, intake and sometimes biokinetic behavior of nuclides in the body. Often, large sets of input data are developed that contain information on attributes and exposure-related parameters for many thousands of individuals in an exposed cohort (1–3).

Exposure conditions modeled in dose reconstructions range from the relatively simple (e.g., controlled external exposures in medicine), to the very complex (e.g., exposures that result from the transport of radioactive substances through environments that change over space and time). Physical phenomena that are modeled in the more complex assessments include transport of radioactive materials in the atmosphere, rivers, ocean environments and terrestrial food chains (1, 4). In those cases, mathematical models to estimate human exposure depend on an in-depth understanding of chemical and physical properties and transport mechanisms of radioactive material as well as an understanding of the modes of exposure that may include external irradiation from radionuclides in air or deposited on surfaces and internal irradiation due to inhalation or ingestion of contaminated food and water. In contrast, exposure assessments in medicine usually require relatively simple models, but often suffer from missing data when reconstructing doses to members of large cohorts exposed in past decades (5).

The relative degree of uncertainty associated with dose estimation is, in part, related to the complexity of the exposure situation, e.g., the chemical and physical form of the radionuclides that one might be exposed to in the environment or, as noted, an outcome of missing (unrecorded) data. Another significant and usual source of uncertainty in dose

²Here, “risk” refers to a statistically derived estimate of the probability of a specific health outcome, e.g., cancer, to occur among exposed persons. The risk can be expressed as excess absolute risk (EAR), which is the additional risk that a radiation dose adds to the usual (background) risk for a disease among unexposed persons or, as excess relative risk (ERR), which is the risk due to exposure relative to unexposed persons minus one.

estimation is the lack of relevant data that applies to each exposed person and the generally low quality of the data that is often available for estimating retrospective exposures.

In past epidemiological investigations requiring dose reconstruction, it was common for the estimates of radiation doses to be provided to biostatisticians as a point estimate (single value) for each individual in the cohort. These dose estimates would usually be considered as “best estimates”, and would form a single vector of doses, i.e., a single set of doses composed of one dose estimate for each individual (6). Biostatisticians would use this information to evaluate the epidemiological dose response using well known statistical fitting methods (7, 8). In so doing, the effect of numerous types of errors and sources of uncertainty in the dose estimates was usually ignored in the evaluation of the epidemiological dose response.

The past practice of ignoring sources of error and uncertainty could be explained, in most cases, by an inadequate understanding on how to account for dosimetric uncertainty in the fitting of the dose response. Failure to account for uncertainties in dose estimates undoubtedly led, in some cases, to poorly justified statements about the doses thought to have been received by the individuals in the cohort and consequently, about the confidence level in estimated risks.

There are several concerns that have been voiced over many years including: 1. the inter-individual variation of true doses among study subjects who have similar exposure attributes; 2. uncertainty of individual doses due to lack of knowledge about the appropriate values of assessment model parameters; and 3. the possibility of varying degrees of systematic errors in a complete set of doses for a cohort (1, 9–14). However, to date, no method has been comprehensively presented in the literature to reconstruct radiation doses in support of an epidemiological study that properly accounts for these difficulties.

Here, we present a method to derive estimates of exposures that capture the uncertainty in individual dose estimates and accounts for possible systematic errors that are shared among members of the entire cohort or among members of subgroups within the cohort. The methods here are similar to those described by Hofer (9). The derivation of multiple vectors of doses for the cohort, each of which may be viewed as possibly true, is an essential intermediate step to characterizing the most reliable estimate of the dose-response relationship (i.e., the radiation risk) and to providing a full and legitimate disclosure of the uncertainty in the estimated risk. For these reasons, we believe the dose estimation strategy described in this article represents a vastly improved methodologic paradigm for providing dose input data to epidemiological analyses.

Literature Review

The need to evaluate exposure assessment uncertainty is widely appreciated but not widely practiced. For example, Jurek *et al.* (15) discuss that errors in exposure measurement (assessment) are rarely accounted for in epidemiologic investigations. A random sampling of articles published in epidemiology journals between 2000–2001 was conducted by the authors, 22 (39%) of 57 articles did not mention exposure measurement error. Sixteen of the remaining 35 articles described qualitatively the effect exposure measurement error could

have had on the study results, while only one article quantified the impact of exposure measurement error on study results using a sensitivity analysis.

Because of the highly quantitative nature of radiation dose assessment, estimation of dosimetric uncertainty is likely more common than is uncertainty for other types of exposures. In the few cases where the uncertainty in dose reconstruction has been addressed explicitly by the dose reconstruction effort, simple uncertainty analyses (one-dimensional analyses that do not distinguish between shared and unshared errors) have primarily been conducted using either Monte Carlo or analytical error propagation methods to produce subjective probability distributions of dose for each and every person in the cohort (3, 16, 17) but often without consideration of dependencies of the uncertainties between subjects. The individual dose distributions were derived from model parameters that included both random and systematic sources of uncertainty and were assumed to represent the state of knowledge of the true dose for each person in the cohort. The doses for individuals in a cohort were often calculated as if the individual dose estimates were independent of one another and that none of the model parameters had identical or similar values for subgroups of persons, i.e., the uncertainties were assumed to be unshared among individuals and systematic sources of shared uncertainty were either nonexistent or negligible. As a result, correlations of dose uncertainty among subgroups of individuals, including the presence of varying degrees of systematic error in the center and spread of the dose distributions for the cohort, were not taken into account. For example, Schafer *et al.* (18) described a process of “accounting for uncertainty in dosimetry” in a study of thyroid cancer after radiation treatments of the scalp. In this instance, the authors reported the error structure was largely Berksonian (i.e., without any shared sources of uncertainty in dose estimation) and that the analysis of the disease and dose data suggested that measurement error in dosimetry had a negligible effect on dose-response estimation.

A number of published articles in the past have discussed distinguishing between uncertainty and variability or imprecision and variability (19–29). Other articles have distinguished between classical and Berkson errors (30) or random and systematic errors (31). One of the earliest references to “two-dimensional Monte Carlo” (2DMC) technique was in an article by T. W. Simon (32), but the article did not contain a detailed explanation of the technique. Glorennec (33) discussed an application of what is called a two-dimensional Monte Carlo simulation in which uncertainty and variability are separated in an analysis of childhood exposure to lead. Similarly, Kentel and Aral (34) describe two-dimensional Monte Carlo approaches with probability distributions used for all uncertain variables, or frequency distributions combined with fuzzy set theory, when parameters of distributions describing stochastic variability of health risks are obtained using expert opinion in the absence of direct measurements. Finally, as noted earlier, Hofer (9) provided excellent background material on understanding uncertainty in the context of exposure assessment and the basis for the methods described here, with somewhat different notational schemes.

To date, a very limited number of health risk studies have attempted to develop multiple realizations of the cohort dose distribution. One early attempt to produce multiple cohort realizations by sharing of source-term related exposure parameters was made by the Hanford

Environmental Dose Reconstruction (35, 36), although the 100 cohort realizations were never used in the Hanford Thyroid Disease Study for which the dosimetry system was developed (37). Drozovitch *et al.* (38, 39) describe the development of 1,000 multiple realizations through the sharing of exposure parameters in two different studies of thyroid cancer in Belarus after the Chernobyl accident. The study of U.S. radiologic technologists developed 1,000 realizations of cohort doses from occupational medical exposure by considering shared errors in the dose reconstruction (40). Finally, Land *et al.* (41) completed a comprehensive dose reconstruction of thyroid exposures from radioactive fallout and simulated 5,000 cohort realizations using the 2DMC method described here.

Definitions and Terminology

Possible errors in exposure assessments in the field of epidemiology and health risk are often called “measurement errors”, though the term is inherently ambiguous. In the physical sciences, for example, measurement error refers to a lack of precision in physically measured “observable” quantities, e.g., laboratory measurements (42). In contrast, in health risk studies, “measurement error”, “misclassification” and “errors in variables” refer to a variety of reasons for discrepancies between true values of variables and their measured values (8, 43). However, it is necessary to understand that in health risk studies, exposures, doses or even exposure-model parameter values are rarely directly measured. For example, exposure to chemical or radiological contaminants in air is sometimes represented by a simple spatially averaged air concentration measurement even though the true metric of exposure is the amount of contaminant inhaled, a quantity that will vary among individuals by location, age, gender, activity level and other factors.

Often, model parameters for a specific exposure scenario are derived from data that may have been collected for other reasons or, at least, are not specific to the exposure assessment for the individual (or individuals) of interest. The quandary is even more significant for the dose or exposure that are also rarely, if ever, measured, and even less often, measured for each individual member of an epidemiological cohort.

Many exposure assessments require complex models that account for many physical processes (1) and have many variables to describe those processes. Therefore, for the reasons described above, we do not advocate the term “measurement error” to describe possible errors in exposure assessments but prefer “uncertainty”, which can include measurement imprecision as well as systematic (shared) uncertainties, and nonrandom (unshared) uncertainties due to imperfect knowledge about quantities having a single true value.

The varied terminology used in the literature on exposure assessments to specify the types of possible errors or sources of uncertainty has led to confusion because of the partial overlap of their definitions and how they are used. Here, we discuss four sets of terms to help clarify the similarities and overlap of each:

1. systematic/random errors;
2. shared/unshared errors;

3. classical/Berkson (or “assignment”) errors; and
4. uncertainty/variability.

Systematic Errors

Systematic errors, as is well known, are those for which estimated, measured or observed values are distributed nonsymmetrically about a true value in such a manner that the expected or mean value of the estimate will be either greater or less than the true value or true mean value for a group (8, 43, 44). Systematic under- or overestimation of true values is known as bias, and this may result in an under- or overestimation of the exposure or dose to a given individual and/or groups of individuals. When systematic errors affect the dose estimates to two or more individuals, they become shared sources of uncertainty. Systematic errors affecting members of numerous cohort subgroups can readily lead to either an under- or overestimation of the true dose response.

In error propagation in the physical sciences, systematic errors are rarely considered as important components of the total error. The reason for this is that if sources of such errors were to be recognized, they would be eliminated through experimental means or accounted for by expressing the quantity of interest by a range of values reflecting the possible range of the systematic error.

Shared Errors

In mathematical models used to reconstruct individual doses to members of a cohort, some parameter values will have an unknown true, fixed value that is shared among members of a subgroup. The uncertainty about this unknown true value is due to a lack of knowledge. For the members of this subgroup, this lack of knowledge of the true value is a shared source of uncertainty affecting the estimate of dose for all individuals. In contrast, some parameters can be treated as varying stochastically between members of a subgroup and/or between subgroups, a source of *unshared* error.

In studies of exposure or health risk involving cohorts, sources of systematic error may be more complex and only pertain to subgroups of a population, considerably complicating the assessment of shared errors. Exposure assessment models often use many parameters and some parameter values may be shared only within a subgroup as a result of the specific exposure attributes of the subgroup. When parameter values are shared, errors in those parameter values are also shared, leading to systematic errors in dose estimates to members of these subgroups.

An exposure assessment model might, for example, depend on parameters that are a function of a variety of covariates, e.g., gender, ethnicity, age group and urban/rural residential location. Fig. 1 shows how each of these attributes is shared within different subgroups of the same cohort. In the Fig. 1 example, exposure model parameters dependent on gender would be shared among female subjects 1, 2, 4, 8 and 9, or among male subjects 3, 5, 6, 7 and 10. In contrast, exposure model parameters such as lifestyle attributes that are dependent on ethnicity might be shared among African American subjects 1, 4, 6 and 7 or among white

subjects 2, 3, 5, 8, 9 and 10. Examples of sharing by age group and residential location (urban/rural) are also shown in Fig. 1.

In general, errors on parameters whose values are shared only among members of a subgroup are much more difficult to recognize and account for compared to systematic errors that affect an entire cohort. As discussed in the following sections, much of the motivation for the 2DMC method is based on situations in which shared errors are substantial and complex among members of cohort subgroups.

Unshared Random Errors

In contrast to systematic (i.e., shared) errors, random errors result in differences in sequential measurements of the same quantity or result in varying estimates of a quantity of interest that is derived from a model, such as a parameter for an exposure assessment model or the dose, itself. Random error in the field of exposure assessment would result in different values for a parameter in repeated trials, repeated calculations or repeated estimation procedures. A subtle point about random error needs to be noted here. If the quantity of interest is a measurement, e.g., a spatial-averaged air concentration of a contaminant, and is to be applied to a subset of the cohort, then the error on the measurement, which would normally be considered as “classical measurement error”, needs to be redefined as a potential systematic error for the subgroup. The distinction is whether the measurement and its associated error are shared among subjects. If random measurement error pertains only to one individual’s dose estimate, the random error is a source of unshared uncertainty. If the error applies to more than one person, it is shared. As will be shown, this distinction has profound implications on the design of the Monte Carlo sampling plan.

Unlike systematic errors, which can result in an increase or decrease of the slope of the dose response, unshared random errors in individual dose estimation can result in attenuation of the slope if the error is of the “classical” type, (i.e., intervariability of true dose among members of the cohort is overestimated) (45, 46).

Unshared Nonrandom Errors

Parameter values that are specific to an individual and independent from values specific to other persons are sources of unshared nonrandom errors. Examples include personal residence history and whether or not the individual consumed milk in the aftermath of a contamination event. When unshared nonrandom errors are described by a probability distribution, this source of uncertainty can easily contribute to inadvertent overestimation of inter-individual variability of true dose. Thus, random and nonrandom sources of unshared errors may contribute to the presence of classical errors in 2DMC dose reconstruction.

Classical/Berkson Errors

For random errors of the Berkson (“assignment”) type, the dose-response slope will not be attenuated given a linear-dose-response model, but estimates of the confidence interval for the dose-response slope will likely be too narrow (45, 46). Random (unshared) errors of the Berkson type are those in which unbiased “assigned” doses (usually the expectation value of dose estimated for members of cohort subgroups sharing the same exposure attributes) are

used as surrogates for an individual's true dose. In simple terms, when dose uncertainties are due to Berkson errors, the assigned dose is assumed to be unbiased (45–48), i.e., it will be equal to the mean of the unknown true doses for all members of a cohort subgroup that share the same exposure attributes of age, gender, diet, residence history, etc. The unknown true individual doses are assumed to vary at random about the unbiased assigned dose. The extent to which the unknown true doses differ from the assigned dose is often left unquantified.

It is often convenient to obtain the unbiased assigned dose from the arithmetic mean dose averaged across all Monte Carlo realizations of an individual's dose. This procedure produces a single cohort vector of individual mean doses. The single vector of individual mean doses is used with conventional regression against the individual's status of disease to produce an unbiased estimate of the dose response, assuming that the error structure is purely Berkson (45–47).

However, when uncertain parameter values used in dose estimation are shared among members of cohort subgroups, systematic errors are present and the estimation of the true mean dose for the subgroup will be an uncertain quantity. Thus, the mean of the individual dose averaged across all Monte Carlo dose realizations may be a biased estimate of the true mean dose for the subgroup. When the individual assigned dose is a biased estimate of the true subgroup mean dose, the assumption of a purely Berkson model is no longer valid.

We note that Berkson and classical errors in individual dose estimation are subtypes of random (unshared) error. Both subtypes have garnered considerable attention in recent years in the risk assessment literature (1, 43, 45, 46) and each has a different impact on the dose response in an epidemiological study. While the unbiased behavior and lack of slope attenuation resulting from Berkson errors has tempted investigators to recast all errors in this form, there are limitations to that strategy as discussed by Thomas *et al.* (43); in particular, restrictions to a linear-disease model and that other problems related to uncertainty in doses, e.g., residual confounding by covariates, exist for Berkson errors, just as for classical errors.

Uncertainty versus Variability

Uncertainty, which arises from a lack of complete knowledge about a true value or a true set of values (1, 8, 12, 13, 44), includes the inability to explain why one individual will have a different dose than another, even though both share the same identifiable exposure attributes of age, gender, residence history, shielding, diet, food sources, etc.

Variability describes a dispersion of values of a quantity. These quantities may be measurements, literature values, observations or true values. For purposes of dose estimation, the term “variability” applies to the dispersion of true values of a model parameter that affects the inter-individual variability of estimates of true dose for members of one or more subgroups in a cohort.

Variability of estimated doses within a cohort will be partially explained by parameters in the dose-reconstruction model that determine differences in dose estimates to individuals and subgroups of individuals due to known differences in identifiable exposure attributes.

As mentioned above, variability is also partially unexplained due to the presence of stochastic processes. Thus, two or more individuals sharing the same exact exposure attributes will have different values of true dose.

The challenge associated with assessments that attempt to estimate true inter-individual variability of dose stems from the possibility that in so doing, the exposure assessment may inadvertently exaggerate (i.e., over-estimate) the variation in true dose among individuals. In this case, the slope of the dose response will be attenuated towards the null, similar to the effects resulting from classical measurement error. More information about the effects on the dose response, referred to in the literature as “measurement errors” or referred to here as “uncertainty”, can be found in several published articles (1, 43, 45, 46, 48–50).

In Table 1, we summarize the various terminologies used in the literature and their inter-relationships. While uncertainty and variability are probably the most recognizable terms, systematic (shared) uncertainties and unshared uncertainties are the most important to distinguish in epidemiologic studies. Systematic, i.e., shared, errors are those that affect subgroups or the entire membership of a cohort, the sources of which may be many. The emphasis here on systematic errors is partly based on the unfamiliarity of many researchers with the concept of shared errors within and among cohort subgroups.

Given the discussion here, it is clear that there are major conceptual differences, as well as implications for dose-response analyses, between errors that are shared within groups compared to errors that are not shared. The 2DMC method is named for its design capability that maintains a separation of shared and unshared sources of error. The following sections discuss how the 2DMC method is to be implemented.

METHODS

In this section, we present the basic concepts of the 2DMC method, a description of how it should be implemented along with an illustration of the method by a simple example, and finally we describe the integration of the 2DMC method within the framework of a dose reconstruction designed to support an epidemiological investigation.

Basic Concepts

To introduce the basic concept of the method, it is necessary to offer a scheme to categorize the parameters of the dose calculation into those that are shared (S) and unshared (U). For this purpose, we define four categories of parameters:

- i. Those that have fixed, but unknown values that are *shared* among members of the entire cohort (given the symbol S_C in this work) or among cohort subgroups (S_S);
- ii. Those that have fixed but uncertain values for specific individuals, i.e., they are *unshared* (U_I);
- iii. Those with well-defined frequency distributions that describe stochastic inter-individual variability for a population of individuals with attributes similar to members of the cohort (U_C) or cohort subgroups (U_S) but are *unshared* with respect to dose estimation for each individual;

- iv. Those parameters that vary stochastically among members of the cohort or cohort subgroups, as in (iii) above, but with uncertainty about the center, spread and shape of the true but imperfectly known frequency distribution describing unshared stochastic variability ($S_C U_C$ or $S_S U_S$). In this latter category, the uncertainty in parameters describing the center, spread and shape of the frequency distribution will be *shared* among all members of the cohort or cohort subgroup that depend on this parameter for dose estimation. However, individual-specific values sampled from each realization of the frequency distribution will be *unshared*.

Table 2 provides additional descriptive detail to define the parameter categories of S_C , S_S , U_C , U_S , U_I , $S_C U_C$ and $S_S U_S$. The importance of assigning every dose-related parameter in an assessment model to its specific category is great, and cannot be overemphasized, since this step definitively determines the sampling scheme in the 2DMC method and greatly simplifies the otherwise extremely difficult task of computing multiple realizations (vectors) of dose for the entire cohort using the 2DMC simulation method.

The following section further describes how shared error is separated from unshared error in parameter categories $S_C U_C$ or $S_S U_S$. For example, such parameters may be specified in the dose-reconstruction model when there is a lack of knowledge about a variable, y , defined as a frequency distribution $F(y|\mu_j, \sigma_j)$ summarizing the variability of values of y over the individuals of a population subgroup j in which each person shares exposure attributes (e.g., age, gender, location, diet, etc.). The frequency distribution $F(y|\mu_j, \sigma_j)$ may be derived or posited, after which it may be used to represent the state of knowledge about the true value for each individual in the cohort subset, i.e., $P(y_n) = F(y|\mu_j, \sigma_j)$, or for all n individuals in subset j . The rationale for this state of knowledge expression is that the individual can be considered as taken at random from the population subgroup and therefore, any one of the values that y_j assumes within this population subgroup is possibly the true individual-specific value with $P(y_n)$ being the subjective probability for the true value not to exceed y_n .

Since $F(y|\mu_j, \sigma_j)$ summarizes the variability of y over individuals within a given population subgroup, its parameters (μ_j, σ_j) that define its center and spread, have single true values that are imprecisely known. The values to be used for (μ_j, σ_j) are uncertain and are the same for all individuals that are in the cohort subset j , i.e., that share the same exposure attributes (e.g., gender, age, location, etc.).

The state of knowledge of (μ_j, σ_j) is expressed by the subjective probability distribution $P(\mu_j, \sigma_j|\theta)$. For example, (μ_j, σ_j) may be the mean value and standard deviation of the frequency distribution of y over the population subgroup j and may be estimated from a random sample of observations or measurements. The subjective probability distribution $P(\mu_j, \sigma_j|\theta)$ may be obtained using expert judgment based on evaluation of indirect data, such as might be derived from the literature representative of comparable conditions.

Implementation of the 2DMC Method

In simple terms, the 2DMC method presented in this article derives M realizations (or sets) of N individual doses. In concept, the 2DMC simulation is implemented by two nested Monte Carlo simulation loops. In programming languages or algorithm science, a *nested*

loop design is an inner loop calculation within an outer loop calculation so that the first pass of the outer loop triggers the inner loop, which executes to completion before returning to the outer loop. The second pass of the outer loop triggers the inner loop and it again executes until completion. This repeats until the outer loop completes a specified number of passes. In the context of the 2DMC, the unshared parameters are simulated within each inner loop pass, while holding the shared parameter values fixed. Within each outer loop pass the shared parameter values are sampled once. The desired sample size of cohort dose realizations is obtained by defining the number of outer loop passes to be equal to the desired sample size. These steps describe the essential design characteristics of the 2DMC.

Correct implementation of the 2DMC design also includes correctly sampling each of the uncertain parameter values, a step dependent on the category to which each parameter is assigned. The 2DMC sampling design for the variable categories of Table 2 is summarized in Table 3 and given in outline form below.

In the outer loop for each of M realizations of the entire cohort:

- a** Sample one value each for all parameters of category S_C ;
- b** sample one value each for all parameters of category S_S ;
- c** sample one pair of values (μ, σ) each for all parameters of category $S_C U_C$ or $S_S U_S$;

Many of the values sampled in steps a and b will be used in the outer loop to compute one value each of several interim results that are then used in the dose computation of the inner loop.

Then, in the inner loop, for each individual in the cohort, $n = 1, \dots, N$:

- d** sample one value each for all parameters with unshared uncertainties of category U_I ;
- e** sample one value each for all parameters of categories $S_C U_C$ or $S_S U_S$ according to the frequency distributions defined by the selection of (μ_j, σ_j) in the outer loop (step c above); and
- f** compute the dose using the set of values for interim results as well as for parameters with shared uncertainties from the outer loop and the values taken for the parameters with unshared uncertainties in the inner loop.

Steps a–c and the inner loop should be repeated M times, in which M is the desired and prespecified number of possibly true sets of N individual dose values for the cohort to be produced. It is important to understand that each of the M sets may be fitted to a single dose-response function, while the entire group of M sets can be used to quantify the overall effect of dose uncertainty on the dose response using full-likelihood dose response methods (51–53).

Here we note that the sampling of the dose model parameters in steps a–e may need to account for state of knowledge dependence between parameters, i.e., they cannot be sampled independently [for example, the pairs (μ, σ) in step c are candidates for state of knowledge

dependence]. State of knowledge dependence requires joint subjective probability distributions, but it is often quantified by correlation coefficients. Not accounting for state of knowledge dependence in steps d and e (and possibly also step b) may lead to inadvertent over- or underestimation of inter-individual variability within each of the M dose vectors. As discussed earlier, overestimation of inter-individual variability is similar, in effect, to classical error and can bias the dose-response analysis towards the null. Algorithms for correlated Monte Carlo sampling are described elsewhere (54). They require sampling steps that are carried out in the outer loop of the 2DMC algorithm.

Steps of an Uncertainty Analysis of Dose Reconstruction Using the 2DMC Method

This section provides a brief description of how the 2DMC method is integrated into the framework of a dose reconstruction where shared error is substantial.

1. Formulate the basic assessment question: *What is the dose D for each of a set of N subjects in a defined cohort?*
2. Formulate the assessment goal given an understanding of the inherent uncertainties: *Derive M possibly true sets of doses for the cohort of N subjects.*
3. Set up a computational version of the assessment model. Typically, this step will consist of a programmed computer algorithm to estimate dose using the 2DMC schema and will contain numerous modeling assumptions, uncertain parameters and making use of several sets of uncertain input data. While this step may seem trivial, in practice, uncertainty analysis of a dose reconstruction would require a thorough investigation of the modeling assumptions, model parameters and input data used.
4. Identify the potentially important uncertain parameters and assign them to their categories (which determine the Monte Carlo sampling scheme).
5. Quantify the states of knowledge of the uncertain parameters and identify and quantify any potentially important state of knowledge dependences between all uncertain quantities identified in step 3.
6. Propagate the states of knowledge through the model by running the 2DMC calculation. Here, M sets of N dose values each are produced through the 2DMC method. Each set is a possibly true representation of the inter-individual variability of true doses within the entire cohort.
7. Produce uncertainty statements. Uncertainty statements can be derived from the M sets for the mean value, standard deviation and any other distribution characteristic of the frequency distribution summarizing the N true individual dose values. Additionally, an empirical subjective probability distribution is available for the true dose of each of the N individuals. This distribution is obtained by collecting the M dose values obtained for the individual over the outer simulation loop. It expresses the state of knowledge for the individual's true dose.
8. Rank the uncertainties with respect to their contribution to dose uncertainty. Uncertainty importance measures can be derived for the mean value, standard

deviation and any other distribution characteristic of the frequency distribution summarizing the variability of the N true individual dose values. This task uses the M sets of N dose values and the M sets of values sampled for the uncertainties in the outer Monte Carlo simulation loop. The ranking indicates where the state of knowledge should be improved in order to reduce the uncertainty about the true values of the distribution characteristics of the N dose values most effectively. Ranking of uncertainties may also be obtained for any individual's dose value by using the M dose values collected over the outer loop and the M values of all uncertainties sampled in the outer and inner loop of the 2DMC simulation and used in the computation of its dose value.

Limiting Inadvertent Introduction of Classical Errors in the 2DMC Simulation Method

When evaluating the spread of frequency distributions that describe inter-individual variability (U_C , U_S) due to stochastic (unexplained) processes and also when using measured or subjectively derived values for individual-specific parameters (U_I), it will be important to identify and remove any excess variability that does not actually occur in nature. Otherwise, inter-individual variability of true dose may be overestimated. In practice, this is a challenging task because the amount of possible overestimation of true inter-individual variability of dose is often unknown.

Classical measurement error, as noted earlier, will tend to overstate the actual variation of parameter values that determine inter-individual variability of individual doses. This effect is undesirable because the overestimation of the true variability results in a bias of the slope of the dose-response function towards the null (45, 46). Thus, if the spread of probability distributions for U_I type parameters and of the frequency distributions for U_C , U_S type parameters systematically leads to overestimation of the inter-individual variability of true dose, their spread must be adjusted (i.e., reduced) so that the inter-individual variability within the M computed vectors of N cohort doses is not unduly affected. The required adjustment is itself uncertain, and therefore the sampling has to be handled in the outer Monte Carlo simulation loop of the 2DMC method (9).

Use of Conditional Individual Mean and Median Doses as an Alternative

The degree to which inadvertent overestimation of inter-individual variability of true dose is associated with each of the 2DMC generated M sets of N individual doses is usually not known. As an alternative procedure, M sets of N conditional individual mean and individual median doses can be generated within the 2DMC simulation in which each set of N individual mean and median doses is conditioned on a fixed set of outer loop parameter values that represent a unique condition of shared uncertainty among members of cohort subgroups. These M sets of N values, termed *conditional individual mean* or *conditional individual median* doses are useful for evaluating the dose response when the potential for excess (i.e., unrealistic) variability among individual doses is present. For this purpose, the inner loop is executed many, (say 100×) times, with sampling of the inner loop restricted to each and every one of the M sets of outer loop parameter values representing systematic/shared uncertainties. This sampling of the inner loop would produce 100 random values of dose for each individual, with all 100 random dose values conditioned on one fixed set of

values selected in the outer loop. From these 100 random inner loop samples of conditional individual doses, a single value of conditional individual mean dose and single value of conditional individual median dose is obtained for all N individuals in the cohort. This process produces M vectors of N conditional individual mean doses and M vectors of N conditional individual median doses. Each of the M vectors of N conditional individual mean and median doses is assumed to be composed of 100% Berkson error [i.e., true doses that vary at random about the assigned (possibly unbiased) conditional mean or median dose].

To take advantage of the M simulated dose vectors in a risk assessment, analysis of all dose vectors is required. Risk assessment methods for that purpose include dose-response analysis of each of the M dose vectors followed by derivation of a weighted average dose response based on the goodness-of-fits or use of one of several full-likelihood or Bayesian methods (51–53).

Extensive testing demonstrated that when dose estimation uncertainties are high, with substantial contributions from shared sources of uncertainty, the most reliable results were obtained using a Bayesian model averaging (BMA) dose-response method coupled with 2DMC multiple dose vectors comprised of conditional individual median doses (55). To compare the reliability of this method with conventional regression, we simulated 180 sets of disease incidence of thyroid nodules from prespecified “true” slopes of a linear dose response using 2DMC dose vectors from the dose models used in the study of Land *et al.* (41). As a metric of reliability, we compared the percentage of test simulations in which the true slope of the dose response was captured by the 95% confidence interval of the estimated slope. For simulation tests with low uncertainty, e.g., for external exposures, we found the BMA method using M vectors of 2DMC simulated individual doses, or conditional individual mean or conditional individual median doses, produced a high inclusion percentage (95.6%). These results were just nominally improved over conventional regression analyses of dose response using a single vector of individual mean or median doses (91 and 94.4%, respectively). However, in simulated tests with significant dose uncertainties, including substantial contributions from shared errors, e.g., for internal exposures, conventional regression using a single vector of individual mean or median doses had an inclusion percentage of only 12.2 or 52.2%, respectively. By contrast, the BMA method using M vectors of 2DMC simulated individual doses produced an inclusion percentage of 70%, while BMA with M vectors of 2DMC conditional individual mean and median doses produced inclusion percentages of 88.9 and 91.1%, respectively.

Example Application of the 2DMC Simulation Method

This example illustrates the basic elements of propagation of uncertainty by the 2DMC method for a simple case in which we consider the model for an individual’s dose D to be the product of four parameters, k_1 , k_2 , k_3 and k_4 [Eq. (1)]. In this example, the goal of the assessment is the estimation of the radiation absorbed dose, D , for each study subject in a cohort of size N and the specific assessment end point is the distribution of absorbed dose to the thyroid gland of female children of 10 years of age at location L due to inhalation of radioiodine from a short-term release of ^{131}I on a specific day. The dose model is Eq. (1):

$$D=k_1 \times k_2 \times k_3 \times k_4 \quad (1)$$

In the absence of uncertainty, a single set (or vector) of dose values (one value per subject) would be adequate to describe the inherent inter-individual variability of the actual doses received by members of the cohort. However, because there is uncertainty in one or more of the model parameters, multiple sets (or vectors) must be produced to fully and appropriately capture the state of knowledge.

In this example, k_1 represents a quantity that has a single true value, but that value is imperfectly known, e.g., the average air concentration (Bq/m³) in the location of interest. While there is only a single true average air concentration, it is uncertain due either to modeling limitations or sparse measurement data. An important point is that the true average value applies to all study subjects at this location. Thus, each value sampled from the subjective probability distribution for k_1 in the outer loop of the 2DMC procedure applies in the inner loop to every individual at this location.

In this example, k_2 is a unitless adjustment factor that accounts for the diminished concentration of radioiodine indoors. In this hypothetical example, children were either outdoors or indoors at the time of the air contamination. There are two values of k_2 : k_{2-out} equal to unity, and k_{2-in} , which is an uncertain parameter that applies to those persons who reply to a questionnaire that they were indoors at the time of the exposure. In reality, k_{2-in} could be described as a frequency distribution with an uncertain center and spread, but in the case of this example, it is assumed to be a fixed but uncertain quantity that applies to every person who remained indoors at the time of the air contamination from the release of ¹³¹I.

The model parameter, k_3 , represents the total volume of inhaled contaminated air (m³) for each subject. The value, for example, might be determined by the inhalation rate $\times$ the exposure time. Though the total inhalation for each subject at the time the contamination cloud passed cannot be retrospectively known with precision, it can be estimated from individual information about the individual's activity (type and intensity of activity) at that time. In this case, individual information on inhalation might be obtained by a questionnaire or an interview with the subject or the subject's parents and the use of a model or population-based datasets that specify inhalation rate as a function of activity level. Because k_3 characterizes inhalation separately for each subject, a unique subjective probability distribution describing its state of knowledge is necessary for each subject.

The last model parameter, k_4 , represents the dose conversion coefficient (DCC), which converts inhaled radioiodine to thyroid dose (mGy per Bq). This coefficient is known to vary substantially among individuals depending on a number of variables including the dietary intake of stable iodine, the mass of the subject's thyroid gland, the subject's metabolic rate and other factors. Since the factors that determine the DCC cannot be known on an individual basis, the frequency distribution of its variation over a population of females of age 10 years must be used to sample from. However, even the distribution of relevant values of the DCC is poorly known, suggesting that both the distribution of the mean (μ) and the variance (σ^2) is uncertain. The frequency distribution of the parameter

described here is chosen to be of lognormal form since it is a parameter that is a product of many factors. Hence, in this example, both the geometric mean (GM) and geometric standard deviation (GSD) of the frequency distribution of k_4 are considered as uncertain. Table 4 and Fig. 2 present a text description and a visual depiction of the four uncertain model parameters, how they are categorized, and how they are sampled according to the 2DMC schema.

As described earlier, one realization of dose to all members of the cohort defines a single dose vector, and is produced by evaluating Eq. (1) once for each of the N subjects using:

- i. a single realization of k_1 to be used for all subjects;
- ii. a single realization of k_{2-out} to be used for all subjects outdoors and a single realization of k_{2in} to be used for all subjects indoors;
- iii. a unique realization of k_3 for each subject; and
- iv. and a unique realization of k_4 for each subject, simulated from a single frequency distribution whose parameters (i.e., GM for k_4 and GSD for k_4) are sampled once for the dose vector in the outer loop.

A second dose vector, i.e., a second realization of a set of individual doses to the entire cohort is produced by repeating steps i–iv. It is important to note that the GM of k_4 and GSD of k_4 used in step iv are newly simulated for each dose vector. The above steps are repeated until the desired number of M vectors of individual doses for the cohort is produced (Fig. 3). As noted earlier, each vector is assumed to be a single possibly true set of individual doses. This example demonstrates, in simple terms, the steps of the 2DMC method.

DISCUSSION

In the past, the uncertainty in the reconstruction of each individual's dose in an epidemiological cohort has often been evaluated independently. Two reasons seem apparent for the relative popularity of that strategy. First, until recent years, there has been only little appreciation of the implications on the dose response from not distinguishing between shared and unshared errors. Second, it seems intuitive to most dose assessment analysts to complete the estimate of dose and uncertainty for each subject before moving to the next.

However, as discussed, such independent uncertainty evaluations ignore the state of knowledge dependence of true values of dose among individual members of a cohort. This dependence is due to shared sources of uncertainty. Calculating individual doses by performing N independent Monte Carlo simulations (one each per subject in the cohort) would be an appropriate procedure, as long as the goal of the assessment is restricted to quantifying the uncertainty of the dose received by each of the individuals, so that the computed individual dose is compared to a limit value to determine the subjective probability for compliance with (or violation of) the limit. However, if the goal of the assessment is to evaluate the relationship between the N computed individual dose values and the disease status of the N individuals in an epidemiological cohort, then producing N independent Monte Carlo simulations would not be a suitable approach. For this purpose, the dose-response estimation requires a possibly true set of N dose values for the individuals

of the cohort and not just N independently sampled possibly true dose values. Due to the shared uncertainties and due to common contributors to uncertainties (expressed, for instance, by correlation coefficients) the states of knowledge of the N individual dose values are dependent and are thus quantified by a joint subjective probability distribution (Fig. 3).

As a consequence, the N dose values cannot be sampled independently according to their marginal distributions when the goal of the dose reconstruction is to simulate a possibly true set of N dose values. If sampled independently, the N dose values will exhibit inter-individual variability that is inappropriately inflated by the variance contributions from shared uncertainties and would be biased with respect to any set of N dose values that could be considered possibly true. What is needed is multiple possibly true vectors of N individual dose values such as those obtained through the 2DMC procedure presented in this article. The overall results of a 2DMC procedure are M sets of N individual dose values with each set of N doses representing a possibly true expression of inter-individual variability of dose. Each set will have a possibly true cohort mean dose, cohort dose variance, and cohort minimum and maximum dose.

The 2DMC procedure offers considerable promise in producing estimates of radiation health risk that account for large and complex uncertainty in dose estimation. Producing multiple sets of possibly true dose vectors implies the necessity of applying each set in the evaluation of the dose response. Several approaches to estimate the dose-response relationship have been proposed, such as a multiple imputation-based method (51), a simple weighted average from multiple dose-response estimates (52), and the Monte Carlo Maximum likelihood (MCML) method (53). In that final step, information about the goodness of fit of the dose response is used to weight each result. This allows for a weighted average overall risk estimate and a more realistic quantification of the overall uncertainty in the derived risk.

Dose Assessment to a Specific Person versus a Set of N Individuals in a Cohort

If the assessment question is focused on estimating the uncertainty in the true dose for a specific individual, uncertainties in all model parameters can be randomly combined in a single Monte Carlo simulation to produce a single probability distribution of possibly true doses for the individual. This strategy, sometimes called a one-dimensional uncertainty analysis, has been common since the 1980s, although we show here that it is inadequate for more complex assessment questions. The resulting distribution of doses from this simple analysis method could be used, for example, to evaluate the likelihood that the individual's true dose would be in compliance with a fixed dose limit.

For dose reconstruction in support of an epidemiological analysis of health risk, however, the more relevant question is: "What is the true set of dose values for the N individuals in the cohort?" The purpose of answering this question is to produce a set of dose values that, along with the observed disease status of each individual, can be used to estimate the dose response in an epidemiological (health risk) study. One could ask whether it would be possible to sample N times from each of the distributions for model parameters of categories S_C , S_S , U_C , U_S , U_I , $S_C U_C$ and $S_S U_S$ and then use the N computed dose values in the dose-response estimation however this would not be possible because computation of the N dose values involves systematic, i.e., shared uncertainties. These shared uncertainties occur in

parameters of categories S_C , S_S , as well as in the uncertainties in the true values for parameters that determine the center and spread of frequency distributions for $S_C U_C$ and $S_S U_S$ parameters. Without correctly apportioning the shared from the unshared errors, it is impossible to deduce a proper set of doses to answer the question posed.

CONCLUSIONS

The 2DMC method was conceptualized and designed as a suitable method for providing a set of M alternative dose cohort dose realizations of cohort dose that express its state of knowledge for dose reconstruction and epidemiologic studies in which shared errors have an important role. The 2DMC approach provides M possibly true sets of individual dose values suitable for dose-response estimation while at the same time providing M possibly true dose values for each individual that are suitable for comparison with dose limits. Uncertainty is expressed by the M possibly true sets of N dose values drawn according to their joint subjective probability distribution. These M sets are obtained by running M times through the outer loop of the 2DMC simulation. Because each of the M sets of N individual doses is a possibly true set of cohort doses, each one of these sets will be suitable for dose-response estimation.

The sample of M possibly true sets of dose values provided by the 2DMC simulation serves as a quantitative expression of dose uncertainty for the cohort. While there may be a perception of considerable difficulty in implementing the 2DMC method, the task is greatly simplified by carefully assigning all the uncertain parameters to one of the defined categories of Table 2, before dose analysis or computer implementation is attempted. It is also worthwhile to note that the computational resources required by the 2DMC method are basically the same as for the simpler and often inadequate approach using N independent Monte Carlo simulations of size M , namely $M \times N$ individual dose computations. However, additional computational resources will be required when producing $M \times N$ conditional individual mean or median doses.

In summary, the 2DMC method provides a robust strategy that can be used in dose reconstructions for epidemiologic studies such that a set of realizations of dose to an entire study cohort can be produced that is a quantitative expression of the state of knowledge of the inter-individual variability of dose within the cohort. While the 2DMC may not be a unique means to this end, we are not currently aware of other strategies that provide this same capability.

Acknowledgments

This work was supported by the National Cancer Institute Intramural Research Program and by the Intra-Agency Agreement between the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, NIAID agreement Y2-AI-5077 and NCI agreement Y3-CO-5117. We would like to acknowledge the contributions to this work by our colleague Robert M. Weinstock (deceased). We also wish to thank our numerous colleagues worldwide, especially those at the National Cancer Institute and the Oak Ridge Center for Risk Analysis for assisting in a variety of ways toward the development of our concepts and understanding, as well as the implementation and presentation of the example material presented here.

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Subject ID	Gender ¹	Ethnicity ²	Age Group ³	Residential location ⁴
1	FM	Afr Am	Adol	R
2	FM	W	Adol	R
4	FM	Afr Am	Adult	U
8	FM	W	Adult	U
9	FM	W	Adol	R
3	M	W	Adol	U
5	M	W	Adult	U
6	M	Afr Am	Adol	U
7	M	Afr Am	Adult	R
10	M	W	Adol	R

Subject ID	Gender	Ethnicity	Age Group	Residential location
1	FM	Afr Am	Adol	R
4	FM	Afr Am	Adult	U
6	M	Afr Am	Adol	U
7	M	Afr Am	Adult	R
2	FM	W	Adol	R
3	M	W	Adol	U
5	M	W	Adult	U
8	FM	W	Adult	U
9	FM	W	Adol	R
10	M	W	Adol	R

Subject ID	Gender	Ethnicity	Age Group	Residential location
1	FM	Afr Am	Adol	R
2	FM	W	Adol	R
3	M	W	Adol	U
6	M	Afr Am	Adol	U
9	FM	W	Adol	R
10	M	W	Adol	R
4	FM	Afr Am	Adult	U
5	M	W	Adult	U
7	M	Afr Am	Adult	R
8	FM	W	Adult	U

Subject ID	Gender	Ethnicity	Age Group	Residential location
1	FM	Afr Am	Adol	R
2	FM	W	Adol	R
7	M	Afr Am	Adult	R
9	FM	W	Adol	R
10	M	W	Adol	R
3	M	W	Adol	U
4	FM	Afr Am	Adult	U
5	M	W	Adult	U
6	M	Afr Am	Adol	U
8	FM	W	Adult	U

¹ FM=female, M=male

² Afr Am = African American, W=white

³ Adol = adolescent

⁴ R=rural, U=urban

FIG. 1.

Example of a Cohort ($n = 10$) That Shares Exposure Attributes and Their Errors Differently among Different Subgroups

FIG. 2.

Graphical representations of state of knowledge distributions for the uncertainties of the example (see text).

FIG. 3.
Cumulative distributions of M possibly true sets of N individual doses produced from the 2DMC dose reconstruction in example (see text).

TABLE 1

Inter-relationships of Error Types

Uncertainty				
Types of errors	Systematic (shared) errors	Random (unshared) errors		
		Berkson	Classical	Nonrandom unshared errors
Description	Uncertainty in models, data, coefficients and assumptions affecting dose estimates to groups and subgroups of individuals. This may include uncertainty in variables that explain subgroup as well as individual differences in dose estimates.	Random uncertainty of unknown true values about an unbiased assigned value (model parameters or dose) to members of a subgroup of individuals sharing similar exposure attributes.	Random uncertainty of estimated, measured or observed values (model parameters or dose) due to measurement error or estimation error.	Fixed true values used to estimate individual dose, which are not shared with other individuals and about which there is imprecise or incomplete knowledge.
Impacts of errors	Results in $\pm$ error in the steepness of slope of dose response; may also affect statistical significance of slope.	No slope attenuation. Confidence interval may be too narrow.	Overstates true variability, results in attenuation of slope towards the null.	If inter-individual variation of true dose is overstated, slope is attenuated towards the null.
				Variation that is partially explained by variables in the exposure model and known individual exposure attributes, and partially determined by random unexplained variation among individuals sharing the same exposure attributes.
				If inter-individual variation of true dose is overstated, slope is attenuated towards the null.

TABLE 2

Definitions of Parameter Categories (Types) Used in the 2DMC Method

Parameter type	Parameter subtype	Values of parameters needed for dose estimation are:	Values of parameters for each realization of a dose vector ^I need to be:	Subjective probability (P) or frequency (F) distribution
S (shared)	S_C	Fixed but unknown, shared by every member in the cohort.	The same value, q_C , for all subjects in the cohort.	The subjective probability distribution $P(q_C \theta_C)$ quantifies the state of knowledge of the true parameter value shared by all individuals in cohort C .
	S_S	Fixed but unknown, shared by all members of the cohort subset.	The same value, q_S , for all subjects in subset S of the cohort.	The subjective probability distribution $P(q_S \theta_S)$ quantifies the state of knowledge of the true parameter value shared by all individuals in subset S .
U (unshared)	U_c	Unexplained inter-individual stochastic variability within the cohort (unshared).	Individual-specific values q varying at random among all subjects in the cohort.	$F(q_i) = F(q_i \gamma_C)$ where γ_C defines the parameters of a well characterized frequency distribution completely summarizing the variability of q_i within a population comparable to the cohort C .
	U_S	Unexplained inter-individual stochastic variability within subgroup S (unshared).	Individual-specific values q_i varying at random among subjects in subset S of the cohort.	$F(q_i) = F(q_i \gamma_S)$ where γ_S defines the parameters of a well characterized frequency distribution completely summarizing the variability of q_i within a population comparable to individuals within subgroup S of the cohort.
	U_I	Fixed but unknown, for a specific individual in the cohort (unshared among subjects).	Individual-specific value q_i .	The subjective probability distribution $P(q_i \theta_i)$ quantifies the state of knowledge of the true parameter value for individual i .
SU (shared and unshared components)	$S_C U_C$	The series of parameters γ_C defining the center, spread and shape of the frequency distributions for S_C type parameters.	Values of γ_C that define $F(q_i \gamma_C)$ for all individuals in the cohort. They are held constant within a cohort dose vector, but will change with each new realization of a cohort dose vector.	The subjective probability distribution $P(\gamma_C \theta)$ quantifies the state of knowledge of the parameters γ_C . It is either derived from values observed for cohorts with members similar to C or based on expert judgment.
	$S_S U_S$	The series of parameters γ_S defining the center, spread and shape of the frequency distributions for S_S type parameters.	Values of γ_S that define $F(q_i \gamma_S)$ for all individuals in an identified subgroup S . They are held constant within a realization of a cohort dose vector, but will change with each new realization of a cohort dose vector.	The subjective probability distribution $P(\gamma_S \theta)$ quantifies the state of knowledge of the parameters γ_S . It is either derived from values observed for cohorts with members similar to S or based on expert judgment.

^I A “dose vector” is a complete possibly true set of doses for the cohort, one dose per person.

TABLE 3

Sampling Plan According to the 2DMC Schema for Variables Assigned to Error Type Categories Discussed in Text and Table 2

	Shared Systematic errors	Unshared	
		Individual-specific errors	Stochastic variability
Description	Uncertainty in models, data, coefficients and assumptions affecting dose estimates to groups and subgroups of individuals (e.g., age, gender, ethnicity).	Fixed true values about which there is imprecise or incomplete knowledge, used for individual dose estimation.	Population-based distributions of varying parameters used as state of knowledge expression for individual dose estimation.
Parameter category	$S_C, S_S, S_C U_C, {}^I S_S U_S, {}^I$	U_I	U_C, U_S
Applied to	Entire cohort or subgroups of cohort	Individuals	Individuals
Where sampled in 2DMC	Outer Loop	Inner loop	Inner loop

^I Mean and variance (or GM and GSD) are sampled in outer loop to determine a frequency distribution that is subsequently sampled on a subgroup or individual basis in the inner loop.

TABLE 4

State of Knowledge about Parameters and Sampling Scheme for Implementation of Example Dose Model [Eq. (1)] using the 2DMC Method

Dose model Parameter	Dose model parameters			Model parameters that are shared (outer loop)			Model parameters that are unshared (inner loop)		
	Model parameter definition	Parameter category	Distribution type	Central tendency	SD, GSD or min:max	How simulated values are applied in model calculation	Distribution type	Central tendency	SD, GSD or min:max
k_1	Average air concentration (Bq/m^3) at location for all subjects	S_C	LN	2,500 (GM)	1.5 (GSD)	Sampled value from outer loop distribution shared by all subjects in cohort	-	-	-
$k_{2\text{-out}}$	Air concentration adjustment factor for outdoors (unitless)	S_S	Constant	1.0	-	Sampled value from outer loop distribution shared among subset of persons outdoors	-	-	-
$k_{2\text{-in}}$	Air concentration adjustment factor for indoors (unitless)	S_S	Uniform	$(\min + \max)/2 = 0.4$	$[0.2, 0.6] \equiv (\min:\max)$	Sampled value from outer loop distribution shared among subset of persons indoors	-	-	-
k_3	Daily inhalation of air per subject (m^3)	U_1 for subject 1	-	-	-	-	Triangular	Mode = 10	$[8, 12] \equiv (\min:\max)$
		U_1 for subject 2	-	-	-	-	Triangular	Mode = 12	$[10, 14] \equiv (\min:\max)$
									Unique value sampled from distribution for subject I in each dose vector
									Unique value

Dose model parameters			Model parameters that are shared (outer loop)		Model parameters that are unshared (inner loop)	
Dose model parameter	Model parameter definition	Parameter category	Distribution type	Central tendency	SD, GSD or min:max	How simulated values are applied in model calculation
k_4		U_l for subject n	-	-	-	Triangular
	Dose conversion coefficient per subject (mGy/Bq)	SUC for GM	Uniform	$(\min + \max)/2 = 3E-3$	$[1.5E-3, 4.5E-3] \equiv (\min:\max)$	GM is sampled in outer loop to define frequency distribution for inner loop sampling
		SUC for GSD	Uniform	$(\min + \max)/2 = 2.0$	$[1.5, 2.5] \equiv (\min:\max)$	GSD is sampled in outer loop to define frequency distribution for inner loop sampling