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Scenario–model–parameter: a new method of cumulative risk uncertainty analysis

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Abstract

The recently developed concepts of aggregate risk and cumulative risk rectify two limitations associated with the classical risk assessment paradigm established in the early 1980s. Aggregate exposure denotes the amount of *one* pollutant available at the biological exchange boundaries from multiple routes of exposure. Cumulative risk assessment is defined as an assessment of risk from the accumulation of a common toxic effect from all routes of exposure to *multiple* chemicals sharing a common mechanism of toxicity. Thus, cumulative risk constitutes an improvement over the classical risk paradigm, which treats exposures from multiple routes as independent events associated with each specific route. Risk assessors formulate complex models and identify many realistic scenarios of exposure that enable them to estimate risks from exposures to multiple pollutants and multiple routes. The increase in complexity of the risk assessment process is likely to increase risk uncertainty. Despite evidence that scenario and model uncertainty contribute to the overall uncertainty of cumulative risk estimates, present uncertainty analysis of risk estimates accounts only for parameter uncertainty and excludes model and scenario uncertainties. This paper provides a synopsis of the risk assessment evolution and associated uncertainty analysis methods. This evolution leads to the concept of the scenario–model–parameter (SMP) cumulative risk uncertainty analysis method. The SMP uncertainty analysis is a multiple step procedure that assesses uncertainty associated with the use of judiciously *selected* scenarios and models of exposure and risk. Ultimately, the SMP uncertainty analysis method compares risk uncertainty estimates determined using all three sources of uncertainty with conventional risk uncertainty estimates obtained using only the parameter source. An example of applying the SMP uncertainty analysis to cumulative risk estimates from exposures to two pesticides indicates that inclusion of scenario and model sources increases uncertainty of risk estimates relative to those estimated using only the parameter source. Changes in uncertainty magnitude may affect decisions made by risk managers.

Keywords: Cumulative risk; Aggregate risk; Uncertainty analysis; Variability; Monte Carlo simulation

1. Introduction

The National Research Council (NRC) instituted the classical risk assessment paradigm, a multiple-step procedure that identifies a hazard and then relates population exposure to one agent with dose and risk (NRC, 1983). However, this conventional risk assessment practice is constrained by the following limitations that could lead to underestimation of risk.

1. Exposures to a pollutant from multiple routes are usually treated as independent events associated with each specific route (EPA, 1999a). Therefore, simultaneous exposures experienced by one person from multiple routes over a period of time are not considered.

2. Exposures to multiple chemicals are often treated as individual events and the combined toxicity effect(s) of simultaneous exposures to multiple chemicals are not addressed.

3. Uncertainty analysis in conventional risk assessment considers only parameter uncertainty. Although both of the other two types of uncertainty (scenario and model) contribute to overall uncertainty, they are frequently assumed

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negligible or ignored (Fayerweather et al., 1999). Failure to account for them could compromise the validity of the outcome and conclusions reached by current methods of estimating risk assessment.

The recently developed concepts of *aggregate* and *cumulative* risks respond to the first and second limitations, respectively (EPA, 1999a, 2000). Risk assessment analysis is evolving as risk assessors formulate models that are more complex, identify many and more realistic scenarios of exposure, and attain new insights that allow the practitioner to estimate risks from exposures to multiple pollutants and multiple routes. This increase in complexity of the risk assessment process is likely to increase risk uncertainties. However, methods to estimate uncertainty associated with risk estimates have remained unchanged. Uncertainty analysis of risk estimates accounts for only parameter uncertainty and excludes model and scenario uncertainties. Risk analysts have not substantiated but assume that model and scenario uncertainties are smaller than parameter uncertainties. In a recent treatment of uncertainty assessment of chemical dose that the authors characterize as "introductory," Hertwich et al. (2000) address all three types of uncertainties. They conclude that scenario and model uncertainty analysis can change dose estimates by several orders of magnitude.

Currently, a specific procedure for a quantitative analysis of scenario or model uncertainty is not available in the literature. A general suggestion regarding analysis of model uncertainty is that risk assessors may use different models to estimate outputs (EPA, 1992a; Hoffman and Hammonds, 1994). The range of outputs can be considered as representing the uncertainty range. A more focused approach that deals specifically with scenario and model uncertainties is known as the distributional approach. This approach has been used in analyses of uncertainty from model structure and alternative assumptions or scenarios (Fayerweather et al., 1999; Evans et al., 1994a,b). The distributional approach divides the risk assessment into a series of decision points called "nodes" that have alternatives. A combination of alternatives from each node constitutes a "tree." Each tree has an assigned probability or "weight" based on expert judgment. This weight is attributed to the risk estimate resulting from each tree. Such results form the final risk distribution. However, the integrity of the final distribution relies heavily on the subjective nature of experts' input. There are also concerns that assigning probabilities to models, i.e., quantifying the possibility of a model to be "correct," is inappropriate (Morgan and Henrion, 1990; Cullen and Frey, 1998). Although the literature does not explicitly refer to scenario uncertainty, it is reasonable to assume that approaches and comments on model uncertainty are applicable to scenario uncertainty.

This paper responds to the need to account for changes in uncertainty magnitude when two, not one, equally valid models and two equally plausible scenarios are used to estimate risk and uncertainty. The objective is to develop a new method that adds model and scenario uncertainty to the conventional parameter uncertainty analysis of the cumulative risk assessment. We call this new inclusive method the scenario–model–parameter (SMP) uncertainty analysis. This paper focuses on the development of the SMP uncertainty analysis as an integral part of the cumulative risk assessment method. We begin with a review of essential concepts involving exposure, dose, and risk, including the new aggregate and cumulative risk concepts, continue with a review of uncertainty classification and uncertainty analysis processes, and conclude by formulating the SMP uncertainty analysis process. We demonstrate the application of this method with results from a related paper on the uncertainty of risk estimates from exposures to chlorpyrifos and diazinon using the National Human Exposure Assessment Survey in Arizona (NHEXAS-AZ) database (Karuchit and Moschandreas, 2001).

2. A synopsis of risk-related concepts

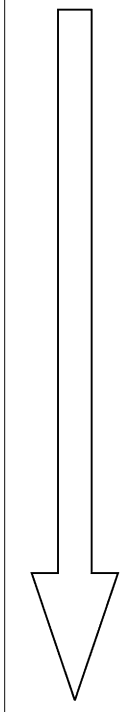
2.1. Exposure and dose

Definitions of exposure, dose and related terms used in this paper are those established in the EPA document "Guidelines for Exposure Assessment" (EPA, 1992a). The basic structure of the flow of an agent from the outer boundary to the receptor target organ and associated definitions are illustrated in Table 1 (EPA, 1992a). The onset of the scheme is the contact of a chemical agent with the outer boundary, which establishes an exposure. The outer boundaries of the inhalation route are the mouth and nose, and the outer boundary of the ingestion route is the mouth. In this scheme, there is no outer boundary of the dermal route, since the skin is the place where absorption takes place, and therefore it is an absorption barrier or exchange boundary, not an outer boundary. The route-specific boundaries, with corresponding chemical transfer process, are shown in Table 2 (EPA, 1992a).

The intake process commences when the chemical moves through the opening of the outer boundary. The amount of the chemical after crossing the outer boundary is called a *potential* dose. Inhalation dose, oral dose and dermal dose are common names for route-specific potential dose (EPA, 1992a). Potential dose is synonymous with *administered* dose. The amount that reaches the exchange boundary is called an *applied* dose (see Table 1). The uptake process takes place at the exchange boundary and involves absorption of the chemical through the skin or exposed tissues. The amount of chemical absorbed is called an *absorbed* dose, while the amount of chemical transported to an individual organ and the amount that reaches it are called a *delivered* dose and a *biologically effective* dose, respectively.

Although the above dose terms signify different quantities, they all have the same unit. The unit of dose has three

Table 1
Exposure and dose scheme (adapted from EPA, 1992a)

Flow direction of chemical into the body	Type of exposure, dose, and boundary	Description
	Exposure	Contact of an agent with the outer boundary of an organism (in this study: human receptor)
	OUTER BOUNDARY	The visible exterior of the person–the skin and the openings into the body.
	Potential dose (also called administered dose)	For inhalation and ingestion route, potential dose is the amount of a chemical that crosses the outer boundary: the amount of chemical in materials ingested (dietary and non-dietary) or in the air breathed. For dermal route, it is the amount of chemical in the bulk material applied to the skin. Route-specific potential dose is called inhalation dose, oral dose, or dermal dose.
	Applied dose	The amount of a substance in contact with the exchange boundaries of an organism and available for absorption. This is the product of potential dose times the bioavailability factor (0-1). *Bioavailability* is the state of being capable of being absorbed and available to interact with the metabolic processes of an organism.
	EXCHANGE BOUNDARY (also called ABSORPTION BARRIER)	Any of the barriers of the body that allow differential diffusion of various substances
	Internal dose (also called absorbed dose)	The amount of substance penetrating across the absorption barriers of an organism
	Delivered dose	The amount of a chemical transported to an individual organ
	Biologically effective dose	The amount of an absorbed chemical that reaches the cells or target site where an adverse effect occurs

different variations: mass of the chemical, mass of the chemical per time, and mass of the chemical per body weight per time. More importantly, the units are common across routes, which is a major advantage when evaluating risk from all routes of exposure, and when comparing contribution of each route to the resulting risk. The generic unit of exposure (Concentration × Time) is usually used for inhalation route only. It is neither practical nor common to use this unit with ingestion and dermal routes. Instead, exposures via these two routes are frequently expressed as potential dose (see, for example, EPA, 1992b, 1993). The unit difference prohibits simple addition of exposure from all three routes. Addition of doses, however, is an established approach as is discussed later.

Table 2
Route-specific boundaries and chemical transfer processes (EPA, 1992a)

Scheme	Process	Inhalation boundary	Ingestion boundary	Dermal boundary[a]
(Hypothetical) outer boundary	Intake	Mouth/nose	Mouth	–
Exchange boundary (absorption barrier)	Uptake	Lung	Gastrointestinal tract	Skin

[a] There is no intake process for dermal route, the skin is the exchange boundary where uptake process takes place (EPA, 1992a).

2.2. Risk and risk assessment

Exposure to harmful chemical agents leads to risk—the probability of suffering adverse effect, e.g., harm or loss. The process of estimating that probability is called risk analysis (LaGrega et al., 1994; Molak, 1997). Risk analysis applied to a particular situation constitutes a risk assessment, which usually estimates the probability of occurrence of human health effects (Molak, 1997). The NRC defines risk assessment as a formalized and structured process that estimates the magnitude, likelihood and uncertainty of environmentally induced health effects (NRC, 1983). Hazard identification, dose–response assessment, exposure assessment and risk characterization are the four elements or steps of risk assessment that constitute the *risk assessment paradigm* (NRC, 1983). Hazard Identification determines whether a particular chemical is causally linked to particular health effects. Dose–response assessment formulates a relation between the magnitude of exposure and the probability of occurrence of the health effects in question. Exposure assessment estimates the extent of human exposure before or after application of regulatory controls. Risk characterization describes the nature and often the magnitude of human risk, including its uncertainty. (NRC, 1983). Details on each element of the risk paradigm and the

significance of exposure and risk assessment with respect to scientific research are found in the literature (e.g., Sexton et al., 1993; NRC, 1983).

2.3. Aggregate and cumulative risk assessment

The *risk assessment paradigm* estimates risks from exposure to one pollutant from multiple routes or multiple pollutants from one route. A paradigm shift was conceived to enable risk assessors to estimate risks from exposures to multiple pollutants from multiple routes. This shift led to the cumulative risk assessment procedure. Thus, the risk assessment evolution begins with the risk assessment paradigm, evolves with the notion of aggregate risk and ends with cumulative risk.

Aggregate risk is the outcome of a three-concept consolidation (EPA, 1999a): (1) Aggregate exposure is the amount of *one* chemical available at the biological exchange boundaries (e.g., respiratory tract, gastrointestinal tract and skin) from multiple routes of exposure. (2) Aggregate dose is the amount of a *single substance* available for interaction with metabolic processes at biologically significant receptors from multiple routes of exposure. (3) Aggregate risk is the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a *single* substance.

The term ‘‘aggregate’’ is the keyword used throughout several recently published EPA guidance documents. The term ‘‘aggregate exposure’’ is not defined as the contact of an agent with the outer boundary of an organism, which is the conventional definition of exposure. Instead, it refers to applied dose—the amount that reaches the exchange boundary. Thus, ‘‘aggregate exposure’’ is the applied dose in all routes of exposure. This peculiar use of the term ‘‘exposure’’ is a concern related to its definition and usage. Indeed, EPA occasionally uses the term ‘‘exposure’’ to refer to dose (e.g., (EPA, 2000, 1992b)). Moreover, simple interpretation of the term aggregate as ‘‘added’’ or ‘‘summed’’ could lead to misconception about how aggregate risk is estimated. In fact, this term is used to denote essential concepts of the new risk assessment approach and deserves careful consideration. Since EPA does not appear to provide an exact definition of this term, for the balance of this paper a practical definition of the term ‘‘aggregate’’ is used to denote two concepts jointly: (1) simultaneous consideration of all routes of exposure and (2) ‘‘individual-by-individual’’ assessment. The first concept is applied to improve the current practice of risk assessment, which typically treats exposure from different routes as independent events (EPA, 1999a). Simultaneous consideration of all routes of exposure contributes to a more realistic risk assessment because a person may be simultaneously exposed to a chemical from multiple routes. The ‘‘individual-by-individual’’ assessment considers exposures that each individual actually experiences, and uses appropriate information regarding time, location, and demographics. These two concepts are applied jointly in an aggregate risk assessment. For each individual, dose is estimated for all routes considered simultaneously, and then combined as an aggregate dose. The combination is based on the dose addition approach, which is explained in the next paragraph, along with the concept of cumulative risk. Aggregate doses, obtained from each individual, are used to formulate the population distribution of aggregate dose. Consequently, the population aggregate risk assessment is based on this distribution.

Although aggregate risk assessment addresses the issue of exposure to multiple routes, it considers only one chemical. The ‘‘aggregate’’ concepts do not address cumulative effects from exposure to multiple chemicals. Cumulative risk assessment incorporates risks from both multiple routes and multiple chemicals. Concepts and methods of cumulative risk assessment are introduced in the EPA document entitled ‘‘Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals that Have a Common Mechanism of Toxicity’’ (EPA, 2000). Fundamentally, the cumulative risk assessment can be viewed as an extension of the aggregate risk assessment. It is defined as an assessment of risk from the accumulation of a common toxic effect from all routes of exposure to multiple substances sharing a common mechanism of toxicity. Common toxic effect refers to the same toxic effect caused by different substances in or at the same organ or tissue (EPA, 2000). Common mechanism of toxicity refers to substances that cause a common toxic effect by the same sequence of biochemical events (EPA, 2000).

Dose addition provides mechanisms and methods to estimate both aggregate risk and cumulative risk. This approach is explained by the following quote (EPA, 2000):

> The application of dose addition is based on the assumption that the chemicals behave similarly in terms of the primary physiologic processes (absorption, metabolism, distribution, elimination), as well as the toxicologic processes. In other words, the chemicals of interest are assumed to behave as if they were dilutions of each other. When applying dose addition methods, the Agency has generally assumed no interactions among the chemicals (i.e., simple additivity) when there is no adequate interaction information.

The margin of exposure (MOE), aggregate risk index (ARI), hazardous index (HI), relative potency factor (RPF) and toxicity equivalency factor (TEF) methods are among the several metrics that help estimate cumulative risk (EPA, 1999a, 2000; Wilkinson et al., 2000). All methods are similar in that they normalize doses of each substance to a common scale (EPA, 2000). The normalized doses are then summed. All methods are considered valid approaches as they are expected to give similar results when certain conditions are assumed and no single method is preferred (EPA, 2000; Wilkinson et al., 2000).

3. Conventional uncertainty analysis of risk estimates

This section reviews the classification and prevailing analysis of risk uncertainty before a new uncertainty analysis procedure is developed. Uncertainty analysis is the analysis of variation or imprecision of the outcome of an assessment (Iman and Helton, 1988). The uncertainty of the outcome is caused by many sources; therefore, uncertainty is generally classified by its sources. Several different classifications of uncertainty are suggested in the literature (EPA, 1992a; Morgan and Henrion, 1990; Bogen, 1990; Cullen and Frey, 1998; Finkel, 1990; IAEA, 1989). In general, there are two commonly used (and often not clearly separated) classifications: (1) scenario, model and parameter uncertainty and (2) uncertainty–variability (U-V).

3.1. Scenario, model and parameter uncertainty

The EPA classifies uncertainty involved in exposure and risk assessments into three types: parameter, scenario and model uncertainty (EPA, 1992a, 1997a,b). The three types of uncertainty, their sources and examples are summarized below.

Parameter uncertainty is the uncertainty regarding parameters (EPA, 1997a). Sources of parameter uncertainty are measurement errors, sampling errors, variability, and the use of surrogate data (EPA, 1997a, 1992a). Measurement errors refer to random errors (imprecision) or systematic errors (bias), while sampling errors are errors from small sample size and/or nonrepresentative samples. Heterogeneity in environmental and exposure-related data includes seasonal variation, spatial variation, variation of human activity patterns by age, gender and geographic location and leads to variability errors. Surrogate data refer to errors from the use of substitute data. The name of this classification requires close attention. The term ‘‘parameter’’ is used to reflect two concepts (EPA, 1997b). The first refers to the distribution parameter—the constants characterizing the probability distribution of a variable (e.g., μ or σ). The second refers to both distribution parameter *and* model variable, where model variable denotes a variable that is an element of a model, such as time, weight, concentration or other variables in an exposure, dose or risk model. In our opinion, the EPA uses the term ‘‘parameter uncertainty’’ where ‘‘parameter’’ denotes both distribution parameter and model variable. This paper uses the term ‘‘distribution parameter’’ or ‘‘model variable’’ instead of ‘‘parameter’’ to avoid possible confusion.

Scenario uncertainty refers to uncertainty associated with missing or incomplete information needed to fully define the exposure and dose (EPA, 1997a). Its sources include descriptive errors, aggregation errors, errors in professional judgment and incomplete analysis (EPA, 1997a, 1992a). Descriptive errors are errors from incorrect or incomplete information, while aggregation errors are spatial or temporal approximations or homogeneity assumptions. Errors in professional judgment are associated with defining appropriate exposure schemes, selecting improper models or determining unrepresentative conditions; and incomplete analysis denotes a source of errors from including or excluding particular exposure scenarios.

Model uncertainty refers to uncertainty from gaps in scientific theory that are necessary to make predictions based on causal inferences (EPA, 1997a). Its sources include modeling errors and relationship errors (EPA, 1997a, 1992a). Simplified representation of reality leads to modeling errors, while errors in correlation among model variables result in relationship errors.

3.2. U-V

An analysis that deals with parameter uncertainty only uses the U-V classification. In this classification, uncertainty is classified as either U or V. V refers to the true heterogeneity, or interindividual variability, attributed to certain characteristics of a population (EPA, 1997b). Other terms used for V in the literature include stochastic uncertainty, aleatory uncertainty and Type A uncertainty (Cullen and Frey, 1998). All parameter uncertainty that is not V is defined as U.

Most analysts prefer distinguishing variability from other types of uncertainty because of its characteristics and ramifications for decision-making in risk assessment. Variability is usually not reducible by further measurement or study, while uncertainty from other sources may be reduced by further measurement (Cullen and Frey, 1998; Burmaster and Wilson, 1996; Haimes and Lambert, 1999). Therefore, differentiating between variability and other types of uncertainty in risk assessment helps decision-makers to focus on appropriate uncertainty reduction measures (EPA, 1997b). Such distinction is fundamental to characterizing uncertainty in the uncertainty analysis (Bogen, 1990; EPA, 1997b; MacIntosh et al., 1995; Rai et al., 1996; Haimes and Lambert, 1999). Burmaster and Wilson (1996) discuss the reason for separating V from U as follows:

> Since V and U arise from different sources, have different interpretations and have different consequences in decision-making, many risk assessors have sought a way to encode and propagate them separately. At the end of a long calculation, it is highly desirable for the risk assessor to be able to segregate the total V from the total U so the risk manager could make appropriate decisions. In particular, the risk manager can do little to reduce the total V in an assessment, but she or he can often reduce the total U in an assessment by commissioning further studies.

Based on its uncertainty type, a model variable can be a U type, V type or both (Bogen, 1990; MacIntosh et al., 1995; Burmaster and Wilson, 1996; Haimes and Lambert, 1999). The concept is best explained by examples. A U variable can

represent the amount of pesticide on a child's hand at a particular time. The amount of pesticide is not varying, but the fixed, true amount is not known because of the lack of knowledge needed to make a perfect measurement. A V variable can represent the grade point average (GPA) of each student in a class. The GPA is known exactly for each student but it varies from one student to another because it represents heterogeneity in the population. An example of a U and V variable is a variable that represents the amount of pesticide on the hands of each student in a class. Its values are uncertain because of the imperfect measurement, and variable because of the heterogeneity in the population. Variables that have *either* U or V are sometimes referred to as "first-order" random variables; while those that have *both* U and V are sometimes referred to as "second-order" random variables (Burmaster and Wilson, 1996). The second-order random variable has a probability distribution that describes its variability, while the distribution parameters are themselves uncertain. Thus, each of the distribution parameters has a specific probability distribution that describes its uncertainty.

3.3. Conventional uncertainty analysis: parameter uncertainty analysis

Uncertainty analysis focuses on model output. Generally, the objectives of an uncertainty analysis are: (1) to evaluate the output uncertainty and (2) to find the relative contribution of each model variable to the output uncertainty. The second objective is commonly referred to as a sensitivity analysis (Iman and Helton, 1988; Hamby, 1994). Analysis results make possible a more informed and sound decision-making process. There are two ways to analyze uncertainty: characterization and assessment (EPA, 1992a). Uncertainty characterization is a qualitative discussion that focuses on the determination of sources of uncertainty and their impact on the model results. Uncertainty assessment is a quantitative analysis of uncertainty.

Parameter uncertainty analysis is the analysis conducted by most analysts at the present time. To analyze parameter uncertainty, four approaches are typically employed: sensitivity analysis, analytical uncertainty propagation, probabilistic uncertainty analysis and classical statistical methods (EPA, 1992a; Cox and Baybutt, 1981; Iman and Helton, 1988; Seiler, 1987; Hamby, 1994; Cullen and Frey, 1998).

4. A new uncertainty analysis of risk estimates

The new inclusive uncertainty analysis is called the SMP uncertainty analysis method. In this section, we present a step-by-step scheme to estimate cumulative risk and the SMP uncertainty. The flow chart of the scheme is illustrated in Fig. 1; it consists of six steps:

Step 1: Identify toxic effects and endpoints
Step 2: Identify the exposure scenarios of concern
Step 3: Develop the dose models
Step 4: Estimate exposure, dose and risk
Step 5: Perform uncertainty analyses
Step 6: Characterize risk

This step-wise scheme is based on fundamental principles of risk assessment and methods suggested by the EPA (EPA, 1999a, 2000). Comparison with the four elements of the early *risk assessment paradigm* indicates that the first two elements of conventional risk assessment—hazard identification and dose–response assessment—are included in the first step of the scheme. Exposure assessment and elements of risk assessment are found in Steps 2, 3 and 4. Risk characterization is put together in the last three steps. Certain steps of the scheme are explained with examples obtained from a study of the Arizona population risk assessment of exposure to pesticides using the NHEXAS-AZ database (Karuchit and Moschandreas, 2001). This risk

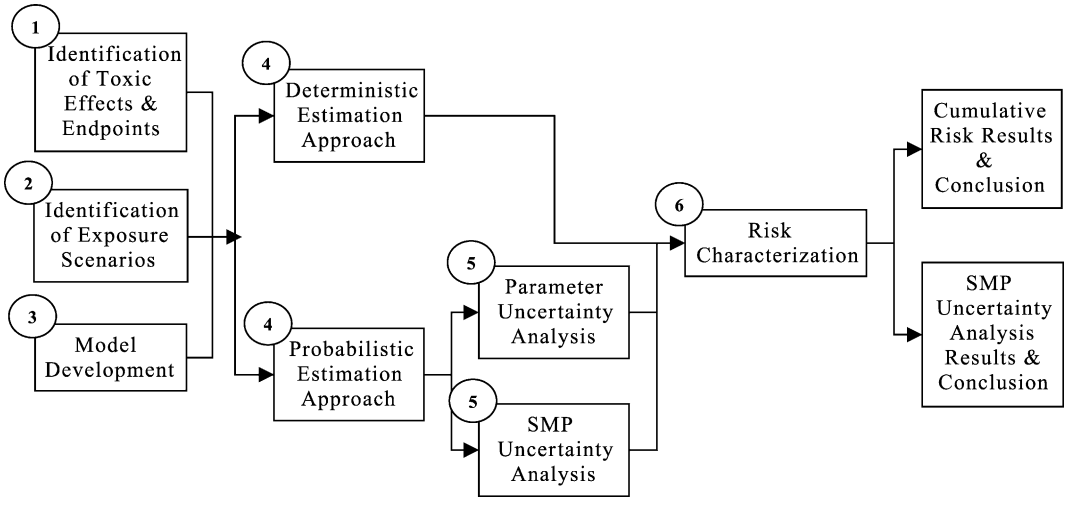


Fig. 1. Flow chart of the scheme.

assessment is an application of the risk assessment uncertainty estimating approach detailed in this paper.

4.1. Identification of toxic effects and endpoints

In the first step, information is gathered regarding toxic effects, toxic endpoints and dose–response relationship of the pollutants investigated. Toxic effects are defined as effects caused by exposure to a chemical that will or can be expected to endanger one's quality of life (EPA, 1999b). Toxic endpoint is the quantitative presentation of a toxic effect at a certain exposure level, e.g., NOAEL and RfD. By definition, cumulative risk assessment is only applicable to pollutants that have common toxic effects and common mechanism of toxicity.

4.2. Identification of the exposure scenarios and exposure models

Exposure scenario is a set of facts, assumptions and inferences about how exposure takes place (EPA, 1992a). EPA's "Standard Operating Procedures (SOPs) for Residential Exposure Assessments" (EPA, 1997c) contains information about major exposure scenarios, which need to be adapted to the pollutants of interest. Not all the listed scenarios need to be included in the final assessment. To perform a risk assessment that is focused and meaningful, the included scenarios must be carefully selected. Criteria for excluding scenarios from a study are not definitive but include: scenarios that have very little possibility of happening; scenarios that are likely to result in trivial amount of subject pollutant dose; and scenarios that have inadequate information to perform an exposure assessment (EPA, 1992a, 2000). Conventional and clear scenarios are identified early in the risk assessment study and are called "baseline." Later in the SMP process, different assumptions are made leading to "alternative" scenarios. Exposure duration is part of an exposure scenario; therefore, duration must be both relevant to the toxic end and realistic. Exposure duration is selected for each of the alternative scenarios. For subpopulations of interest, an assessment uses the baseline scenarios with only subjects from the subpopulation groups that are likely to be exposed to pollutants of interest.

Identification of models for estimating exposure and potential dose, Step 3, are pollutant dependent and are developed on the basis of several existing examples found in the literature. Dose models employ the indirect method of exposure estimation, also known as the scenario estimation approach.

4.3. Estimation of exposure, dose and risk

Efforts in this step begin with estimating exposure to subject pollutants and continue with estimating dose and risk caused by the exposure. While measurement of exposure is possible for certain pollutants, it is not possible for all pollutants. When exposure measurement is not feasible, concentration and questionnaire data are combined to estimate exposures using the indirect method. Concentration measurements are generally obtained from field studies. Subject information (e.g., time and frequency of contact, food consumption, and area of surfaces contacted) and other exposure factors can be obtained from questionnaire data, literature or assumptions. A typical assumption for the estimation is that the subjects' exposure to pollutant concentrations in air, food and surfaces takes place according to each scenario defined over periods relevant for the manifestation of a toxic effect. A concentration measured in a bulk medium is assumed homogeneous and not varying over the time of interest. For each subject and environment, medium sampling must take place at the same time and the exposure, dose and risk of pollutants assessed must have the same mechanism of toxicity (EPA, 2000).

Usually, certain pollutant concentrations are censored values because they are assigned values below the limit of detection (LOD) of their perspective measurement instrument. Below LOD measurements are generally assigned one of three values (zero, the LOD value or a value half the LOD value) or they can be assigned values using the robust method. The robust method generates "fill-in" values for those below LOD values according to the distribution of the above-LOD values (Helsel, 1990; Moschandreas et al., 2001). The "fill-in" values are then assigned randomly. This assignment is permanent for all analyses for a given database.

Cumulative risk can be estimated using either the deterministic or the probabilistic approach; each approach has advantages and limitations. We recommend both approaches to gain insights in the assessment and to make use of extant databases. The deterministic approach is the fundamental estimation approach that is appropriate for the application of the "individual-by-individual" concept of the aggregate and cumulative risk assessment. In this approach, each subject's data are used with appropriate models to estimate pollutant and route-specific dose, and then the risk metric. Therefore, each risk metric is calculated using the dose estimates that belong to one and the *same* subject. However, this approach has two major limitations. First, it cannot provide as much information about the variation, i.e., uncertainty, of the estimated results as the probabilistic approach. Second, the estimation can be performed only on those subjects with a complete set of data—those who have exposure estimates for all pollutants and all routes. In other words, subject measurements must be available for all media (e.g., indoor air, food, floor dust, sill wipe and yard soil) along with other relevant data needed for the dose estimations. In this study, such subjects constitute the cumulative assessment group (CAG). Although this may be the case for a few databases generated for research purposes, this is not generally the case for all subjects and all media for most databases that are medium specific. The probabilistic estimation approach is used to overcome these limitations.

The probabilistic approach uses a probability distribution to represent each model variable instead of a point estimate, a single value. The estimation is performed using the Monte Carlo method—a statistical sampling method for obtaining the probability distribution of the possible outcomes of a model (EPA, 1997b). The probability distribution of each variable is developed using all available subject data. Consequently, the information used in the assessment is not limited only to the information from those subjects who have a complete set of data. The other advantage of the probabilistic approach relates to its greater potential and ability to analyze uncertainty. The limitation of the probabilistic approach relates to its inability to accommodate the "individual-by-individual" assessment concept. The probabilistic approach eliminates the identity of each subject in the simulation process because the probability distribution of a variable is the distribution of the population, and individual subjects used to formulate the distribution are no longer discernible. Therefore, the dose and risk are not estimated for each sample subject, but for all that combine to represent possible outcomes. Although the estimation does not conform to the strict cumulative risk assessment concept, it estimates the population distribution of the output, given that the probability distributions of the model variables are good representation of the population.

4.3.1. Deterministic method

The deterministic method employs appropriate dose models discussed in the previous step to estimate dose for all routes, inhalation, dietary ingestion, dermal absorption and nondietary ingestion. To estimate aggregate risk and cumulative risk, the HI method is used in the NHEXAS-AZ risk assessment of exposure to two pesticides: chlorpyrifos and diazinon. The application of this method is explained below (EPA, 1999a, 2000; Patrick, 1994; Mumtaz, 1995).

The HI of each subject is the summation of the hazardous quotient (HQ) of the subject, which is calculated using the following equation:

$$\mathrm{HQ}_{r,p} = \frac{D_{r,p}}{\mathrm{RfD}_{r,p}} \tag{1}$$

where r denotes exposure route, p denotes pesticide; $D_{r,p}$ is the estimated potential dose of pesticide p from route r for each subject; $\mathrm{RfD}_{r,p}$ is the reference dose of pesticide p and route r.

The aggregate HI for each pesticide is the sum of its HQs in all routes, and the cumulative HI is the sum of all HQs. Thus, the aggregate HI is estimated by:

$$\mathrm{HI}_{A,\mathrm{chlorpyrifos}} = \sum_r \mathrm{HQ}_{r,1} \tag{2}$$

$$\mathrm{HI}_{A,\mathrm{diazinon}} = \sum_r \mathrm{HQ}_{r,2} \tag{3}$$

The cumulative HI of each of the CAG subject is estimated by:

$$\mathrm{HI}_{\mathrm{CAG}} = \sum_r \sum_p \mathrm{HQ}_{r,p} = \mathrm{HI}_{A,\mathrm{chlorpyrifos}} + \mathrm{HI}_{A,\mathrm{diazinon}} \tag{4}$$

4.3.2. Probabilistic method

The primary purpose of probabilistic risk estimation is to analyze uncertainty and its sources as they associate with risk estimates. The probabilistic analysis may be performed using the Monte Carlo method and one of several commercial software packages such as the Crystal Ball (Sargent and Wainwright, 1996). Based on the deterministic dose and risk estimation models, the first step in a probabilistic analysis is the formulation of a probability distribution for each model variable.

Model variables can be classified into two classes: (1) variables with measured values from field studies and (2) variables with assigned values, either surrogates or assumed. For the purpose of sensitivity analysis, variables estimated from submodels involving observed data and surrogate or assumed data should be segregated in the probabilistic analysis models. In other words, each variable is substituted by its submodel variables. Thus, a probability function is developed for such variables based on observed data without the effect of surrogate or assumed data. The segregation has the benefit of improving the characterization of the input variables and the identification of significant contributors in model outputs.

To obtain credible outputs, significant correlation among input variables must be taken into account in the Monte Carlo simulation. Rank correlation coefficients are calculated for each pair of input variables to determine if significant correlation exists. Selected significant correlation coefficients are then specified in the simulations. When a correlation between variables is defined, the simulation program (e.g., in Crystal Ball) generates random numbers for each variable from its probability distribution and uses the correlation coefficient to rearrange the numbers to achieve the specified correlation.

4.3.2.1. Monte Carlo methods in probabilistic uncertainty analysis. The Monte Carlo method is a statistical sampling method for obtaining the probability distribution of the possible outcomes of a model (EPA, 1997b). The Monte Carlo simulation process is described as follows (Cox and Baybutt, 1981; Sargent and Wainwright, 1996). Let $\alpha_1 \ldots \alpha_m$ be the input variables of a model. First, each of the independent variables are assigned a probability distribution. Second, the simulation process selects one value for each variable based on its probability distribution. This step is repeated a large number of times, N. Consequently, N sets of values $(\alpha_1^{(i)} \ldots \alpha_m^{(i)})$, $i = 1$ to N, are obtained and the corresponding model outputs, $Y^{(i)}$, $i = 1$ to N, are calculated. The distribution of N outputs represents the population distribution. The uncertainty of the output can be examined

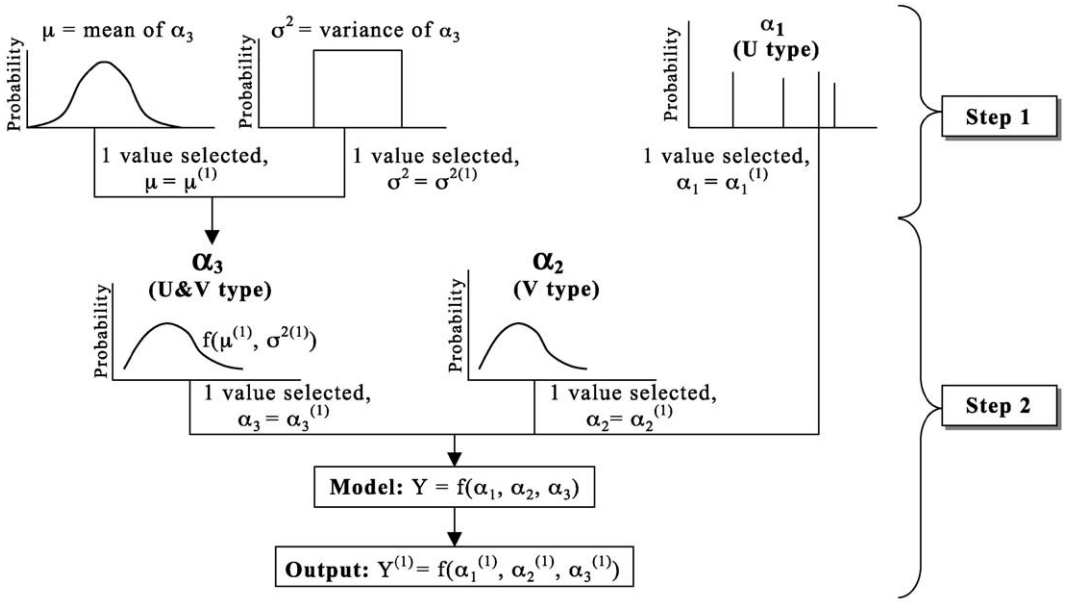


Fig. 2. Illustration of the 2-D Monte Carlo simulation in Steps 1 and 2.

using several statistics, including the standard error (S.E.) of the mean and the confidence interval (CI) of the mean or a specific percentile. Alternatively, the Monte Carlo method can be described as a process where N sets of values are obtained from a joint distribution of all of the input variables, and N corresponding model outputs are calculated (Cullen and Frey, 1998).

An advanced technique called the two-dimensional (2-D) Monte Carlo simulation is used with an uncertainty analysis that requires variability to be distinguished from other types of uncertainty (Bogen and Spear, 1987; IAEA, 1989; Hoffman and Hammonds, 1994; MacIntosh et al., 1995; Burmaster and Wilson, 1996). Also known as "nesting" or "double looping," this simulation technique has an ability to separately propagate the two types of uncertainty (Cullen and Frey, 1998). The two steps in the process are explained using the following example. Let Y be the assessment endpoint, which is a function of three variables: α_1 (a U

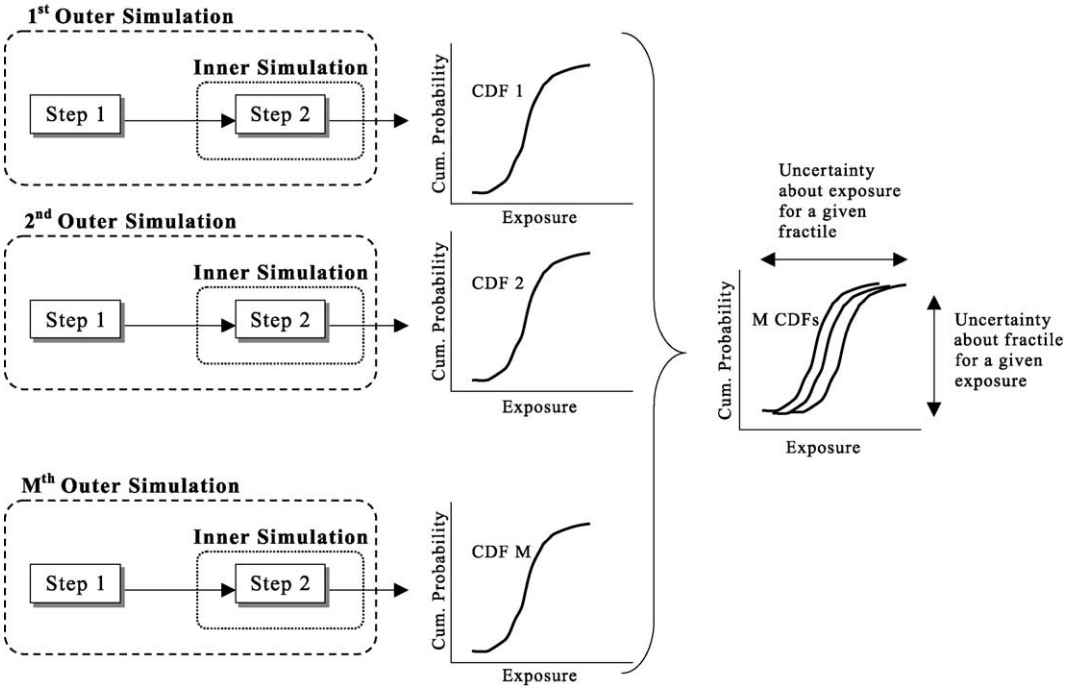


Fig. 3. Illustration of the 2-D Monte Carlo simulation process (adapted from MacIntosh et al., 1995).

variable), α_2 (a V variable) and α_3 (a U and V variable). The 2-D Monte Carlo simulation of this assessment is illustrated in Figs. 2 and 3.

Step 1: (1) A random value is selected for α_1, a U-variable, from its probability distribution. (2) The U and V variable α_3 has a probability distribution that describes its variability, while its distribution parameters—the mean and variance—are uncertain. A random value is selected for each of the parameters from their probability distributions. The selected pair of mean and variance characterizes a distribution for α_3.

Step 2: (1) A random value is selected for α_2, a V variable, from its probability distribution. (2) A random value is selected for α_3 from its probability distribution, which is obtained from Step 1. (3) The value of α_1 (selected in Step 1) and the values of α_2 and α_3 (both selected in Step 2) are used to estimate one output value.

Fig. 2 illustrates the two steps. Step 2 is called an "inner" simulation. It is repeated a large number of times, N. In each repetition, the value of α_1 is fixed at the same value selected in Step 1, only the values of α_2 and α_3 vary. The simulation that includes one run of Step 1 and N runs of Step 2 is called an "outer" simulation. It creates one output distribution of size N. A large number of outer simulation runs, M, are performed to create a family of distributions (see Fig. 3). For the outer simulations, the value of α_1 is different from one run to the other as a result of Step 1 selection of each run. The uncertainty associated with a statistic (e.g., mean or percentile) of the outcomes can be estimated from its S.E., obtained from the family of M distributions. Furthermore, the uncertainty about the percentile associated with a certain output value can be estimated from the range of the percentiles corresponding to that value. The range is obtained from the M distributions.

4.4. Uncertainty analysis

4.4.1. Parameter uncertainty analysis

Sensitivity analysis and probabilistic uncertainty analysis are two approaches used to analyze parameter uncertainty in this study. The former finds the relative contribution of each model input to the change in the output, while the latter evaluates the variation or imprecision in the output. The flow chart for parameter uncertainty analysis is shown in Fig. 4. In the NHEXAS-AZ pesticide risk assessment, seven simulation modules with appropriate models are used:

Module 1: Chlorpyrifos inhalation dose ($D_{1,1}$) estimation
Module 2: Chlorpyrifos ingestion dose ($D_{2,1}$) estimation
Module 3: Chlorpyrifos dermal dose ($D_{3,1}$) estimation
Module 4: Diazinon inhalation dose ($D_{1,2}$) estimation
Module 5: Diazinon ingestion dose ($D_{2,2}$) estimation
Module 6: Diazinon dermal dose ($D_{3,2}$) estimation
Module 7: Cumulative hazardous index (HI_{CAG}) estimation

All input variables in dose models are V types; their values vary from one individual to another in any population of interest. The only input variable that is U type is the RfD variable for each case. A reference dose is a benchmark dose level that applies to every individual in the population, but its true or rather "best" value is unknown for each pollutant; such a variable is a U type.

Simulations of Modules 1 through 6 are performed using conventional Monte Carlo methods. The number of runs

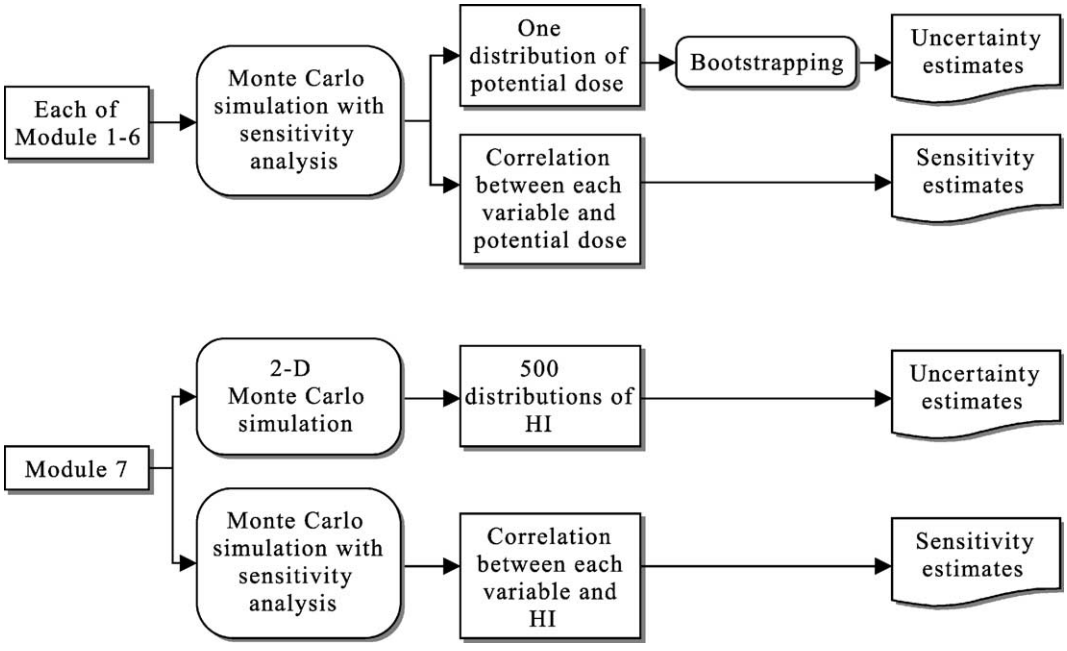


Fig. 4. The flow chart of the parameter uncertainty analysis.

used for each simulation was 5000. Selection of the number of runs in the simulation is usually based on the computing limitation and acceptable level of precision for the most concerned results (Cullen and Frey, 1998). In this study, we focus our attention on the high-end of the output distributions, particularly the 90th percentile values. Thus, the number of runs selected was based on the numerical stability of this output. As the number of runs increases, the 90th percentile estimate stabilizes, i.e., closes in on nearly constant values. The use of 5000 runs ensures that numerical stability of the 90th percentile was achieved.

For Modules 1 through 6, analyses of the variation of outputs used S.E. of the 90th percentile estimates that are calculated using the nonparametric Bootstrap method (Efron and Tibshirani, 1993; Montgomery and Runger, 1999). Five hundred bootstrap samples, each consisting of 5000 values, are randomly sampled with replacement from the original set of 5000 output values. Then, the 90th percentile is estimated for each bootstrap sample, resulting in 500 values of the 90th percentile, from which one obtains the S.E. and other statistics of the 90th percentile. The sensitivity analysis of each module is performed simultaneously with the Monte Carlo simulation using the rank correlation coefficient method. Model variables with high correlation values, R, have a significant impact on the corresponding model output. The model output and the rank correlation coefficient, R, between values of each variable and the output are calculated simultaneously. Therefore, two outputs are obtained at the end of the simulation: a distribution of 5000 output values and the coefficient values. The coefficients of all input variables are ranked and compared to identify the highly sensitive variables.

2-D Monte Carlo simulations are performed for estimating the cumulative hazardous index of the CAG subjects (HI_{CAG}), Module 7, which consists of U variables and V variables. The number of runs used is equal to 5000 and 500 for the inner and the outer simulation, respectively. For the inner simulation, 5000 runs ensure the numerical stability of the 90th percentile. For the outer simulation, the criterion for selecting the number of runs is based on the concept of nonparametric tolerance limits used by Hoffman and Hammonds (1994). The concept provides a method to find the sample size M needed to create an interval that contains at least a proportion q of the population, with a $1-\alpha$ confidence level (Conover, 1980; Montgomery and Runger, 1999). Usually, the lower and upper tolerance limits are set to be the smallest and largest sample values, respectively. Using $q=0.99$ and $\alpha=0.05$, a sample size of $M=473$ runs was calculated for our example. Thus, with 500 outer simulation runs, there is at least a .95 probability that at least 99% of the population of the estimate is between the smallest and largest values of the set of values obtained. Therefore, in the 2-D simulation, 500 distributions of the cumulative hazardous indexes (HI_{CAG}) were obtained. The mean and median of each percentile and their uncertainty were then estimated.

4.4.2. The SMP uncertainty analysis

At present, there is no standard method for quantitatively analyzing these types of uncertainty. The SMP uncertainty analysis method presented in this section was developed to incorporate scenario and model uncertainties in the uncertainty analysis in risk assessment. The SMP uncertainty analysis can be performed on any statistic of interest. The process is best explained by an example. In the Arizona pesticide risk assessment, the SMP analysis was performed on the cumulative hazardous index, HI_{CAG}, of a subject population. It begins by dividing the analysis procedure used to obtain HI_{CAG} into a series of decision points with alternatives. Two decision points, each with two alternatives, are identified and illustrated as a "decision tree" in Fig. 5.

4.4.2.1. Decision point #1. The first decision point is the selection of the method used to develop the probability distribution of model variables. Since the uncertainty in the

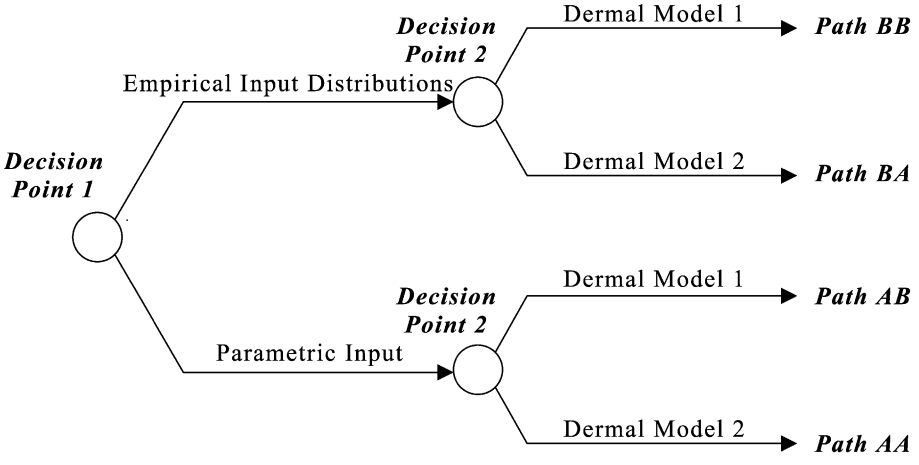


Fig. 5. The "decision tree" of the SMP uncertainty analysis.

model output is propagated from uncertainty in each of the model variables, the probability distribution must be developed with appropriate methods. Two commonly used methods are parametric distributions, i.e., standard distributions that fit observations such as normal, lognormal and others, or empirical distributions, i.e., a histogram of study observations. The use of empirical distributions has certain advantages and some limitations. Using parametric distributions also has its benefits. With their own advantages and disadvantages, there is no general agreement as to which method is preferred (EPA, 1997b). The use of different methods is likely to result in significantly different outputs and output uncertainties. Therefore, the decision made at this point is an important source of scenario uncertainty, and is considered as the first decision point of the SMP uncertainty analysis. The alternatives of this decision point are the empirical distribution method (baseline scenario) and the parametric distribution method (alternative scenario).

4.4.2.2. Decision point #2. The second decision point is the selection of a model for estimation of dose. Unlike models for inhalation or ingestion route, dermal dose models are more complex and take different forms. Thus, continuing with an explanation of the SMP method by example, we select as the baseline model that is suggested by the EPA in its publication entitled "Research Solicitation: Human Exposure Assessment" (EPA, 1993). It uses concentration data in three media (floor dust, sill wipe and yard soil) and combines the data with subjects' characteristics to estimate dermal potential dose. However, the model does not take into consideration information from hand wipe or dermal wipe. Dermal wipe data are available for both pesticides in the NHEXAS-AZ database. With the use of a general EPA dose model (EPA, 1992a), the dermal wipe data can be used to obtain different, but equally credible, estimates of dermal dose. These estimates are independent of the floor dust, sill wipe or yard soil data. The decision made regarding the model selection is an important source of both scenario and model uncertainty, and is considered as the second decision point of the SMP uncertainty analysis. The alternatives of this point are the dermal model 1 (baseline model) and the dermal model 2 (alternative model). The two models are summarized in Appendix A.

After establishing two alternatives for each of the two decision points, four analysis paths must be considered for estimating the SMP uncertainty (Fig. 5):

- Path BB: Use empirical input distributions and dermal model 1
- Path BA: Use empirical input distributions and dermal model 2
- Path AB: Use parametric input distributions and dermal model 1
- Path AA: Use parametric input distributions and dermal Model 2

The path with baseline decision for both decision points is Path BB. For each analysis path, the 2-D Monte Carlo simulation of Module 7 is performed using 5000 inner simulation runs and 500 outer simulation runs. Therefore, we obtained 500 distributions of HI_{CAG} estimates and 500 90th percentile estimates from each analysis path. Based on these outputs, the uncertainty of 90th percentile estimates was estimated and compared among different analysis paths. At this stage, uncertainty estimated for each analysis path is the parameter uncertainty only.

Four uncertainty analyses were established to investigate the effect of inclusion of scenario or model uncertainty:

- Analysis P: Analysis that considers parameter uncertainty only
- Analysis SP: Analysis that considers scenario and parameter uncertainties
- Analysis MP: Analysis that considers model and parameter uncertainties
- Analysis SMP: Analysis that considers scenario, model and parameter uncertainties

Analysis P accounts for only parameter uncertainty and ignores scenario and model uncertainties. It has only one analysis path, Path BB. Analysis SP considers both scenario and parameter uncertainties; therefore, it has two analysis paths: BB and AB. In essence, this analysis assumes that the two paths are equally suitable for the assessment, and assigns equal chance to each path to be used. In a similar fashion, Scenario MP considers both model and parameter uncertainties, and assumes that Paths BB and BA have equal probability to be used in the assessment. Finally, Analysis SMP considers all three types of uncertainties, and assumes that all analysis paths are equally appropriate for the assessment.

The scheme used to obtain estimates from each analysis is explained below. Analysis P is performed to obtain 500 estimates of two statistics, the median and the 90th percentile, using Path BB only. Analysis SP is performed to obtain 250 estimates of the two statistics from each of the two analysis Paths BB and AB. Analysis MP is performed to obtain 250 estimates of the two statistics from each of the two analysis Paths BB and BA. Finally, Analysis SMP is performed to obtain 125 estimates of the two statistics from each of the four analysis paths. The distributions of each statistic are compared among analyses. The mean and variance values estimated by each analysis are tested for equality. Ultimately, the relative change of risk uncertainty that accounts for only parameter uncertainty to risk uncertainty that jointly accounts for scenario, model and parameter uncertainty is estimated using the 95% tolerance limits range.

4.5. Risk characterization

The findings from the risk assessment are integrated in this final assessment step. Issues discussed in the risk

characterization include risk estimates and associated uncertainties, and comparisons of risks among subpopulations. Additionally, risk characterization identifies variables that significantly affect the outcomes in each simulation module, or alternatives in the assessment that could change the conclusions reached. Finally, risk characterization elaborates on the results of the SMP uncertainty analysis and substantiates all findings to assist and support the decision-making process.

5. Discussion

The SMP uncertainty analysis method is not intended to quantify all uncertainty that exists, i.e., uncertainty from all imaginable scenarios and all published models. Instead, it provides the mechanism that allows judiciously selected scenarios and/or model uncertainty sources to be included in the analysis. Ultimately, the SMP uncertainty analysis compares the uncertainty based on all selected uncertainty sources with that based on parameter uncertainty alone to ascertain if ignoring certain sources of errors would change the conclusions reached. This method, therefore, allows the risk assessor to be all-inclusive and consider all appropriate sources of uncertainty. If the SMP estimate is significantly larger than the conventional estimate, the decision may be affected. Conversely, if the SMP result is *not* significantly larger than that of the conventional analysis, it is reassuring to know that the uncertainty estimate is not sensitive to the additional uncertainty sources included in the SMP analysis.

Selection of alternative models and scenarios as sources of uncertainty is the nucleus of the SMP analysis process; it must focus on realistic and practicable alternatives. Clearly, exposure scenario selection depends on the population, pollutant, subject population and relevant information about the population. Recall that cumulative risk requires that the pollutants share a common toxic end and the same mechanism of adverse effect. Such information and associated factors can be obtained from the literature. The models selected for use and their alternatives depend on the exposure route. It is important to note that the literature contains many additional models, making the appropriate choice of alternative models a critical concern.

Performance of the SMP uncertainty analysis requires performance of a risk assessment study. Therefore, it requires identification of one or more databases, information on the subject population and subpopulations, selection of model and scenario uncertainty sources and factors that will be used in the performance of the research. In the work presented in the related paper, the SMP uncertainty method was applied using NHEXAS-AZ database. It is one among the very few multiple pollutant, multiple route exposure, risk studies sponsored by a consortium of federal agencies led by the EPA. NHEXAS-AZ consists of comprehensive subject information obtained from a multiple stage survey using six different questionnaires on demographic, housing, food consumption, time budget and other pertinent information. Most databases, however, are not as comprehensive and therefore are likely to result in larger uncertainties than those found in this application.

Analysis results obtained from the NHEXAS-AZ pesticide risk assessment indicate that inclusion of scenario uncertainty source into the process for estimating cumulative risk uncertainty increases overall uncertainty. The uncertainty of the 90th percentile estimate of HI_{CAG}—as measured by its 95% tolerance limits range—increases almost threefold compared to the output uncertainty that considers only parameter uncertainty. Inclusion of the model uncertainty source increases the uncertainty of this statistic by 56%, and inclusion of both the scenario and model uncertainty sources increases uncertainty by nearly a factor of two. Similar results are obtained when the uncertainty is measured by the range of the 95% confidence level of the mean of the 90th percentile HI_{CAG}.

Clearly, this result confirms that the scenario and model uncertainty sources are significant contributors to overall uncertainty of the outcome of the assessment. When both are ignored, the 90th percentile of HI_{CAG} is not likely to be near the level of concern: 95% of the estimates are between 0.22 and 0.70. When the scenario uncertainty source is included, i.e., the use of parametric distribution is considered an equally appropriate alternative as the use of empirical distribution, the abovementioned conclusion about the 90th percentile of HI_{CAG} changes substantially. Both analysis scenarios that include the scenario uncertainty yield tolerance limits range that extend more than 1.50, which means that the 90th percentile HI_{CAG} could exceed the level of concern. Thus, the cumulative risk assessment process that includes two different but realistic scenarios with two different but equally feasible models may lead to risk estimates that have substantively different uncertainty from that estimated with conventional estimating risk uncertainty methods.

Appendix A. Two dermal dose models

A.1. Dermal dose model 1

The baseline dermal models for estimating potential dose are as follows (Moschandreas et al., 2001):

$$\text{Dose}: \quad \mathrm{PD}_{\mathrm{der},t} = E_{\mathrm{der},t} \times \mathrm{BW}^{-1} \times 10^3 \tag{A.1}$$

$$\text{Exposure}: \quad E_{\mathrm{der},t} = E_{\mathrm{der},r} + E_{\mathrm{der},y} \tag{A.2}$$

$$E_{\mathrm{der},r} = \sum_s \left[C_{\mathrm{D}s} \times A_{ps} \times T_{\mathrm{p}s} \times (1 - \mathrm{DO}_{ps})\right] \tag{A.3}$$

$$E_{\mathrm{der},r} = \sum_s \left[C_{\mathrm{S}s} \times ((S_{ps} \times \mathrm{SA}_{ps}) - \mathrm{SO}_{ps})\right] \times M \tag{A.4}$$

$PD_{der,t}$ is the total dermal potential dose of the pesticide of each subject (ng/kg day)
$E_{der,t}$ is the total dermal exposure to a pesticide of each subject (μg/day)
BW is the body weight of the subject (kg)
$E_{der,r}$ is the dermal exposure to the pesticide in dislodgeable surface residue of each subject (μg/day)
$E_{der,y}$ is the dermal exposure to the pesticide in soil of each subject (μg/day)
s is the type of surfaces contacted per day. Dislodgeable surfaces residue data in the NHEXAS database were obtained from two surfaces: floor surface and window sill surface. The latter is assumed representative of residue from "nonfloor" surfaces, i.e., surfaces other than the floor in the house, such as furniture surfaces. For Eq. (A.3), $s=1$ for floor surface and $s=2$ for nonfloor surface. For Eq. (A.4), $s=1$ for yard soil surface.
C_{Ds} is the pesticide concentration of dislodgeable surface residue on surface s (μg/m2)
A_s is the surface area of surface s contacted by the subject (m2/day)
T_{ps} is the transfer proportion of surface s by the subject, proportion
DO_{ps} is the proportion of dislodgeable residue of surface s transferred to oral route by the subject via hands, food and objects; proportion
C_{Ss} is the pesticide concentration in soil surface s (μg/g)
S_{ps} is the soil from surface s covering on skin of the subject (g/m2·day)
SA_{ps} is the body surface area of the subject exposed to surface s (m2)
SO_{ps} is the amount of soil from surface s covering on skin that is transferred to oral route by the subject (g/day)
M is the matrix effect of soil, proportion

A.2. Dermal dose model 2

The general EPA dose model calculates the average daily potential dose, ADD_{pot}, by (EPA, 1992a,b, 1997a):

$$ADD_{pot}(\text{ng/kg day}) = \frac{\text{Total Potential Dose (ng)}}{\text{Body Weight (kg)} \times \text{Averaging Time (day)}} \quad (A.5)$$

To use the general EPA dose model, a scenario of dermal exposure may be defined as follows. Since pesticide residue on each subject's skin comes from both outdoor (e.g., soil) and indoor (e.g., floor and furniture surfaces) sources, the exposure duration is assumed 24 h per day. Therefore, the total potential dose is the potential dose integrated over the 1-day duration and the averaging time used in the model is 1 day. Furthermore, it is assumed that the pesticide mass is distributed uniformly over the exposed body surface area and is represented by the dermal wipe concentration. Therefore, the total potential dose is estimated by the dermal wipe concentration times the exposed body surface area:

$$\text{Total Potential Dose} = C_{hand} \times SA_{ps} \times 10^3 \quad (A.6)$$

C_{hand} is the pesticide concentration in the dermal wipe sample (μg/m^2)
SA_{ps} is the body surface area of the subject exposed to surface s (m^2)

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