

Cumulative & Aggregate Risk
Evaluation System

CARES

Conceptual Model

January 8, 1999

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Cumulative & Aggregate Risk Evaluation System

Executive Summary

The Food Quality Protection Act now mandates that the US Environmental Protection Agency consider both aggregate and cumulative risks. Aggregate assessments account for multiple sources and routes of exposure for a single chemical. Cumulative assessments combine exposures to two or more chemicals that share a common mechanism of toxicity. A stand-alone, comprehensive computer program is needed to perform the mandated assessments. To address this need, the Cumulative and Aggregate Risk Evaluation System (CARES) will be developed and deployed through a cooperative effort of stakeholders, including government, industry, and environmental groups.

CARES will utilize currently accepted and other relevant databases to evaluate potential risk from dietary, drinking water, and residential sources. Risks will be calculated deterministically for Tier 1 screening, and probabilistically using Monte Carlo simulation of individuals for higher tier analyses. CARES will allow users to estimate doses and risks from acute, short term, intermediate duration, and lifetime exposures. A unique feature of CARES allows a risk manager to interactively query the program and identify the factors contributing to the highest percentiles of risk.

CARES will be user-friendly, fast, intuitive, easy to use, and capable of providing accurate and reliable tabular and graphical reports. Documentation, manuals and tutorials accompanying CARES will be of high caliber and easy to use. Version control will be accomplished by official release of approved versions.

CARES validation will include both testing and verification of the underlying exposure assessment models as well as the testing and documentation associated with the system life cycle approach.

Source code will be published and electronically available to permit continued testing and improvement. In contrast to proprietary software, open code promotes acceptance and trust amongst stakeholders by allowing independent validation and the addition of case-specific features to keep pace with scientific developments.



Cumulative & Aggregate Risk Evaluation System

The Food Quality Protection Act (1) now mandates that the US Environmental Protection Agency consider the aggregate exposure and the associated risk of single chemicals arising from multiple sources and routes. Furthermore, when two or more chemicals share a common mechanism of toxicity, then the cumulative dose and risks from exposure to these chemicals must be estimated.

Currently, there is no single software tool capable of integrating the necessary exposure and hazard information into a comprehensive risk assessment. Thus, neither the government nor the regulated community has the tools needed to make decisions or to evaluate compliance with the Food Quality Protection Act. The purpose of the CARES Project (Cumulative and Aggregate Risk Evaluation System) is to develop a software tool that will be made available to all users at a nominal cost. The source code for the program will be published electronically. This will make the methods used transparent and verifiable by the entire scientific community interested in evaluating risks associated with pesticide exposure. The success of this project depends upon a cooperative effort of all stakeholders (industry, government, advocacy groups, consultants, and academia).

1.0 What Will CARES Do?

CARES will permit stakeholders to produce transparent and reproducible risk assessments. These assessments will evaluate exposure from dietary, drinking water, residential and all other non-occupational sources for which there are any applicable, relevant, and appropriate databases. Acute, short term, intermediate duration, and lifetime exposures and risks will be evaluated.

EPA risk assessments generally have been deterministic in nature and have used single point estimates to characterize hazard, exposure, and risk. The uncertainty introduced by using point estimates (whether average or upper bound estimates) increases with the number of variables used to calculate the estimates (2, 3). The use of distributional methods has been recommended by the National Research Council (4) for the estimation of dietary intake of pesticides, and by the EPA (5) for assessments of exposures from all sources. CARES will calculate doses deterministically for Tier 1 screening or probabilistically using Monte Carlo simulation for higher tier analyses.

This paper will not discuss or attempt to resolve the difficult scientific and data requirement issues involved in conducting aggregate and cumulative risk assessments. Several workshops (6, 7), stakeholder meetings (8), and scientific debates (9) have attempted to deal with these complex issues. CARES, however, will present a range of approaches that will encompass current scientific debate using databases that are currently available or in the process of being developed.

1.1 How to Aggregate

Aggregate assessments account for multiple sources and routes of exposure for a single chemical. CARES calculates source and route-specific doses for an individual on the same day and combines them in a biologically appropriate fashion to obtain the aggregate dose. For higher tier assessments, distributional analyses using Monte Carlo simulation provide a scientifically defensible methodology for combining doses from multiple sources. The technique involves constructing a probability distribution for the aggregate dose in a specified population by examining the aggregate doses for different individuals.

Aggregate risk can be characterized by a distribution of a risk metric such as margin of exposure (Figure 1). The entire distribution of aggregate dose and its risk metric is then compared to a safety standard in order to reach a risk management decision. (See Glossary for definitions and acronyms.)

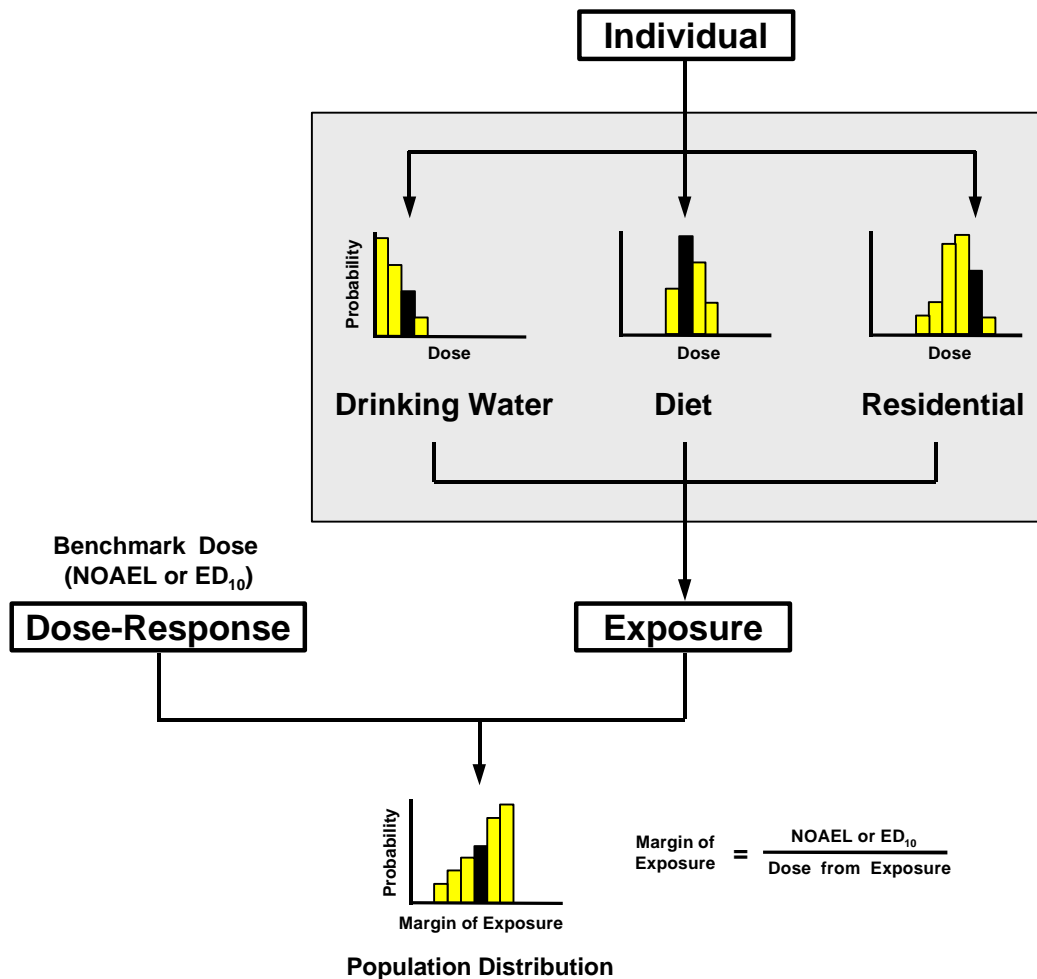


Figure 1. Aggregate Risk Characterization

All pesticide exposures should be aggregated or cumulated for the same individual one day at a time. The individual's daily dose should be calculated in a temporal, spatial, and demographically consistent manner. For example, an individual's dose from exposure on a specific day is aggregated only over that individual's food consumption and drinking water ingestion on that day and not food consumption from one day aggregated with drinking water ingestion on a different day. Similarly, a dose from drinking water in the northwest is not aggregated with the dose from a residential exposure in the southeast. Age, gender, season, region, race, pregnancy/lactating status, and other demographic factors will be treated consistently. If the dose from exposure is defined as the biologically effective dose and the level of the biologically effective dose on a day depends on the doses in preceding days, then CARES can incorporate and reflect that dependence.

1.2 How to Cumulate

In cumulative risk assessments, the potential exposure to two or more chemicals is described as a joint probability distribution rather than as independent probability distributions for each chemical alone. For example, if residues of two chemicals are found on apples, then the cumulative dose resulting from apple consumption should reflect the joint occurrence of the two residue concentrations on the same apple. It would be incorrect to combine the residue of one chemical present on one apple with the residue of the second chemical on a different apple unless the apples were consumed as a blended commodity.

Figure 2 illustrates a case where Chemicals A and B share a common mechanism of toxicity and a cumulative risk assessment is appropriate. In this example, the probability of the joint occurrence of residues for Chemical A and B is determined and the concomitant exposure to both chemicals is cumulated. The composite distributions of doses for Chemicals A and B can then be expressed as a combined distribution of toxicologically equivalent doses. This is accomplished by multiplying the dose for each chemical by an appropriate toxicity equivalency factor (Table 1). Alternatively, the Hazard Index (HI) or Margin of Exposures (MOE) for each chemical can be combined using the equations presented in Table 1.

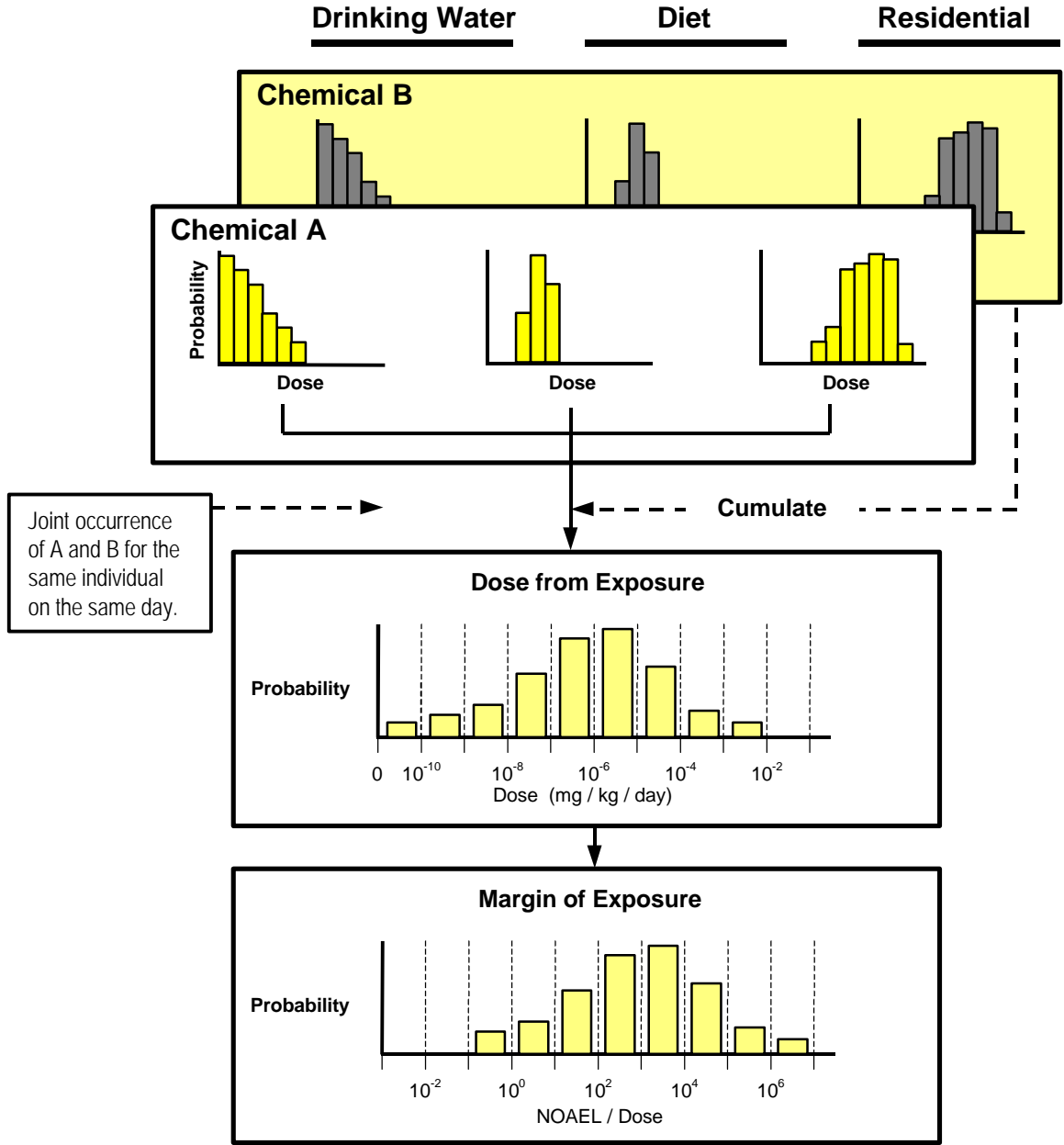


Figure 2. Illustration of a Cumulative Risk for Multiple Chemical Exposure

1.3 How to Combine Doses

The mathematical combination of doses across routes and across chemicals depends upon establishing a common ground for comparison. CARES will initially allow the user to select one of the three alternative combinatorial approaches identified in Table 1, and others as they become available.

Table 1. Alternate Methods for Calculating Cumulative Risk

Method	Description	Cumulative Equation
Toxicity Equivalency Factor (TEF)	The hazard of each chemical in the class is expressed relative to a standard and then the dose is adjusted for relative potency.	$(\text{Dose}_a \times \text{TEF}_a) + (\text{Dose}_b \times \text{TEF}_b) + \dots$
Margin of Exposure (MOE)	The MOE is calculated for each chemical as a ratio of its benchmark dose to the dose from exposure. The MOEs are then combined.	$\frac{1}{(1/\text{MOE}_a) + (1/\text{MOE}_b) + \dots}$
Hazard Index (HI)	The HI is calculated as a ratio of the dose from exposure to the reference dose. The HIs are summed.	$\text{Dose}_a / \text{RfD}_a + \text{Dose}_b / \text{RfD}_b + \dots$

The Toxicity Equivalency Factor approach has been successfully used when one chemical provides a reference point for all members of a class of chemicals sharing a common mechanism. For example, the toxic equivalency of dioxin congeners has been expressed relative to TCDD (10).

The Margin of Exposure (MOE) approach (11) is preferred when the benchmark doses (e.g., NOAELs) for compounds sharing a common mechanism are based upon the same toxicity endpoint or biochemical surrogate, evaluated in the same species by the same route of administration and for the same duration of exposure. Experimental error in accurately defining the NOAEL can be controlled by standardizing the magnitude of response across studies by using the best estimate of the 10% Effective Dose (ED_{10}) as the benchmark dose.

The use of the Hazard Index method (12) is acceptable if the RfD for each chemical is based upon similar studies and the magnitude of the uncertainty factors are the same. When the studies or the uncertainty factors used in determining the RfD are different, then combining the hazard indices is not desirable because it is not possible to separate uncertainty from variability in the final risk distribution.

1.4 Multi-Tier Risk Assessment Approach

The Food Quality Protection Act has focused attention on aggregate and cumulative risk. CARES will be the software that conserves resources and expedites regulatory decision making for simple cases, but is scientifically rigorous enough to deal with complex cases. A multi-tier assessment approach is accommodated; the lowest tier uses default assumptions and single point (deterministic) estimates of exposure, hazard, and risk. Tier 2 assessments utilize a combination of deterministic and probabilistic (distributional) data while Tier 3 assessments rely predominantly on distributions.

Tier 1 screening methods can be used to conduct preliminary assessments. If necessary, the risk assessor can perform higher tier analyses, which are more realistic because they make use of all available data. Sensitivity analyses, uncertainty analyses, and Monte Carlo simulation techniques allow the risk assessor to identify those factors that contribute most significantly to the final risk distribution. Thus, the factors that impact risk can be identified and data can be collected for a higher tier analysis if the chemical fails to pass the Tier 1 screen.

Table 2 provides a list of factors commonly used in assessing the risk from exposure to pesticides. This Table does not list all factors that might be utilized in a comprehensive risk assessment, only a representative few that are frequently encountered. A more detailed listing of such factors and the values commonly assigned to them can be found in the EPA Exposure Factors Handbook (13), the American Industrial Health Council Exposure Factors Sourcebook (14), and the literature.

1.5 Additional Unique CARES Features

An important feature of CARES allows the risk assessor to interactively query the program to characterize aggregate and cumulative risks. For example, the risk assessor can (i) identify the factors contributing to the highest percentiles of risk, (ii) identify the relative contributions of exposure to chemicals from different sources and routes, and (iii) identify the age, gender, geographic, and demographic characteristics of more highly exposed individuals.

CARES will incorporate time profiles of the dose from exposure (e.g., calendar profiles consisting of the dose from exposure on each of the 365 days in a year). Calendar specific time profiles are used to determine dose characteristics (e.g., the average daily dose calculated as a moving or "rolling" average) for an acute, short-term (e.g., a week), intermediate-term (e.g., a month), or chronic (e.g., one year or 70 years) exposure duration. CARES will also take into account any correlation between an individual's dose across days.

With CARES, it will be possible to calculate the individual's daily dose using the most biologically relevant dose scale (applied, delivered, or biologically effective dose). CARES will also be able to make use of absorption, distribution, metabolism, and elimination data to quantify the time dependent magnitude of the dose at critical targets using physiologically-based pharmacokinetic information.

Table 2. Typical Exposure, Dose, and Risk Assessment Factors

Exposure Factors	Tier 1 (Default Value)	Tier 2	Tier 3
Exposure Factors for Dietary & Water			
Residue Level	Diet (Tolerance) Water (MCL)	»»»	Residue Distribution
Market Share	Constant (100%)		Variable (Year, Region)
Food Intake	Mean (DRES)		Distribution
Water Intake	Constant (2 liters/day)		Distribution
Exposure Duration	Continuous (Daily)		Population Linked Distribution
Population Linked	Constant (100%)		Link to Population
Exposure Factors for Residential & Lawn Uses			
Dislodgeable Residue • Turf • Residential	Constant (20%) Constant (20%)	»»»	Distribution
Penetration Factors • Clothing/Type • Dermal	Constant (50%) Constant (100%)		Distribution Experimentally Determined
Use Pattern • Duration • Frequency • Reentry Interval	Constant (Daily) Constant (Specific) Constant (Immediate)		Distribution
Population Linked	Constant (100%)		Link to Population
Dose Factors			
Body Weight	Constant (70 kg)	»»»	Distribution
Body Surface Area	Constant (21,110 cm ²)		Weight-Dependent Variable
Respiration Rate	Constant (29 l/min)		Weight-Dependent Variable
Dose Scaling Factor	Constant (BW) ^{3/4}		Physiologically-Based
Metabolism	No Metabolism		Pharmacokinetic Model
Hazard Factors			
Benchmark Dose • RfD • ED ₁₀ , LED ₁₀	Constant (Chemical Specific)	»»»	Distribution (Chemical Specific)
Relative Potency • Q ₁ * • TEFs	Constant (Chemical Specific)		Distribution (Chemical Specific)
Accumulation Factors			
Conditional Probability • Multi-source • Multi-chemical	1.0 1.0	»»»	Distribution (Chemical Specific)
Uncertainty Factor vs. Percentiles of Probability Distributions			
Health Standard	Use Uncertainty Factor (e.g., 10, 100, 1000)	»»»	Use Percentile of Distribution (e.g., 95 th percentile)

2.0 How Will CARES Do It?

The programming technology known as “object-oriented programming” provides a near-ideal match to the requirements of the CARES program. CARES will be constructed from modules called objects. Objects can consist of program control components (e.g., to control Monte Carlo simulation), computer models of discrete parts of the real world (e.g., a crop, a cow or herd of cows, a field), or interactions between objects (e.g., between a cow and a field). The algorithms included in the objects simulate the behavior of chemicals in the real-world object that they represent, or the movement of chemicals between such objects.

The program will have a “connect-the-boxes” graphical interface that allows construction of the system to be modeled, where each box will represent one of the objects (Figure 3).

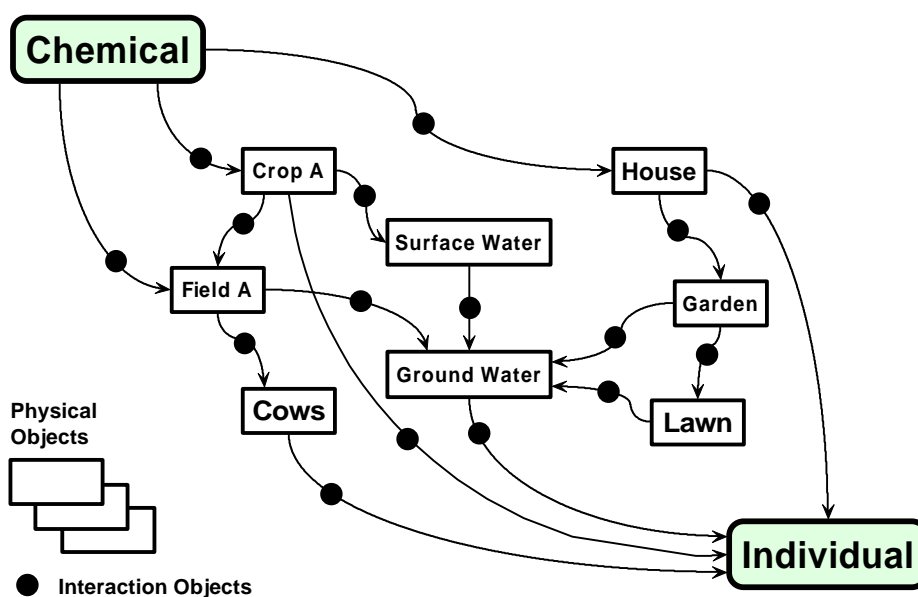


Figure 3. Schematic Representation of Object Oriented Program Structure

Once the user has described the system to be modeled using the graphical interface, the program will compute doses iteratively. The dose of a chemical will be calculated for hypothetical individuals. These individuals will be randomly selected by a population generator (Figure 4) that uses a hierarchical decision tree based on demographic descriptors.

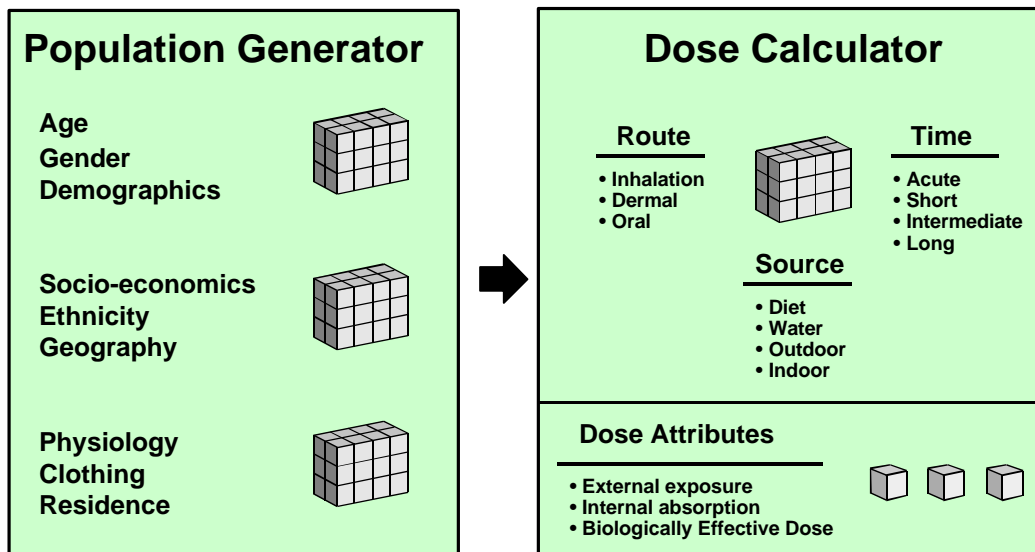


Figure 4. Population Generator and Dose Calculator

The dose calculator will be linked to objects and databases as illustrated in Figure 5. Individual daily doses are aggregated from multiple sources or cumulated for chemicals sharing a common mechanism of toxicity. The program will be able to calculate the daily dose either deterministically or probabilistically. Using object-oriented programming techniques, all the inputs to the program may be specified as either constants or probability distributions. The probability distributions will come from empirical measurements (e.g., residue concentrations in water) or from fitted functions (e.g., age-dependent body weight distributions).

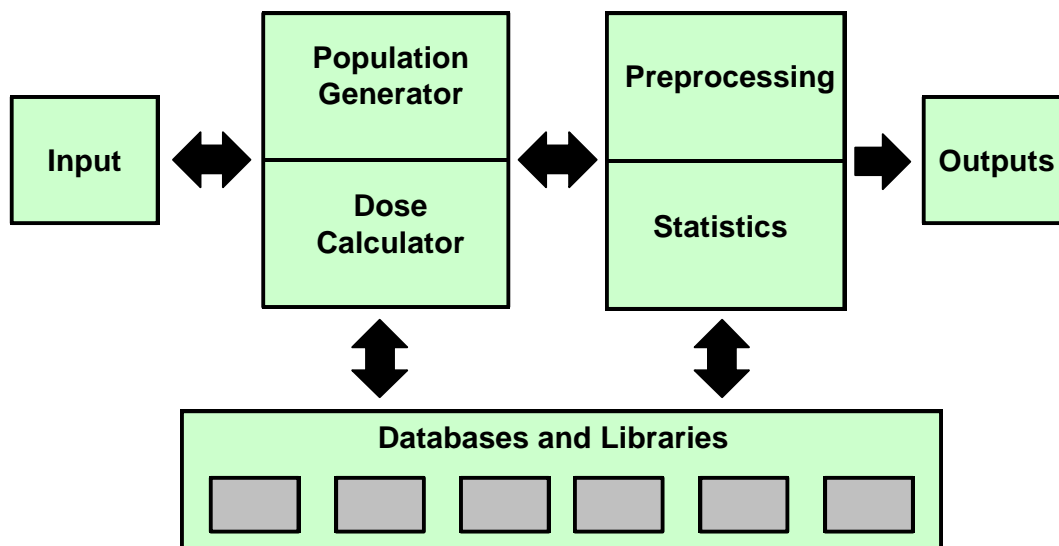


Figure 5. Process Flow Diagram

For Monte Carlo simulations, the program draws repeatedly from observed distributions, and for each repetition it calculates risks. Using nested program loops, it evaluates population variability and/or uncertainty in the calculated results. Population variability may be taken into account by evaluating every member of a reference population (e.g., all entries in a database), or by randomly selecting from subsets of the general population.

To increase the usefulness of the program, it will incorporate various techniques that will enhance the interpretation of the results. Extreme results will be identified and tagged, allowing the user to trace back from the risk distribution to evaluate the contributing source(s). Sensitivity analyses will allow the user to identify critical inputs and the most efficient ways to make the assessment more accurate. Differential analysis will permit the user to identify the influence of changes in any input on the output.

The modularity inherent in object-oriented programming allows for straightforward replacement of each object. It also allows the user to define components for substitution or addition into the program, such as adding a proprietary model.

3.0 To What Databases Will CARES Be Linked?

Data used to perform CARES assessments will be obtained from three general sources: user input, survey data, and peer-reviewed literature. The first type of data source will enable assessments of new chemicals using proprietary information. The second type of data source includes large sets of survey information collected by industry, government agencies, and the research community that do not appear in the peer-reviewed literature (e.g., pesticide commodity profiles, food consumption rates, and exposure factors). The third type of data source is information contained in scientific papers published in peer-reviewed journals.

Four fundamental types of databases will be used by CARES:

- **Product Attributes:** Product-specific information on physical-chemical characteristics, transport and fate, and existing or proposed formulations and applications.
- **Occurrence Data:** Measurements of pesticide levels in various environmental media.
- **Exposure Factors Data:** Pesticide use and usage, and frequency and duration of human contact with pesticides (e.g., food and water consumption and activity patterns).
- **Evaluation Criteria Data:** Data needed to assess the reliability of estimated exposures and risks through comparison to biological markers of exposure and health effects as reported in the scientific literature.

The program modules described above will be linked to validated databases that contain information required to perform aggregate and cumulative risk assessments. To ensure data quality, CARES will:

- document the data sources;
- collect information needed to define data quality;
- rank the quality of the data (e.g., gold, silver, bronze);
- identify unsatisfactory data; and
- utilize the best data.

4.0 How Will CARES be Validated?

CARES validation will include both the testing and documentation associated with the system life cycle approach (system validation) as well as testing and verification of the underlying exposure assessment model and its representation (model validation).

System validation will be conducted and documented using the system life cycle approach illustrated schematically in Figure 6. Full documentation of the validation process (as listed in Table 3) will be maintained and made available when CARES versions are released for use.

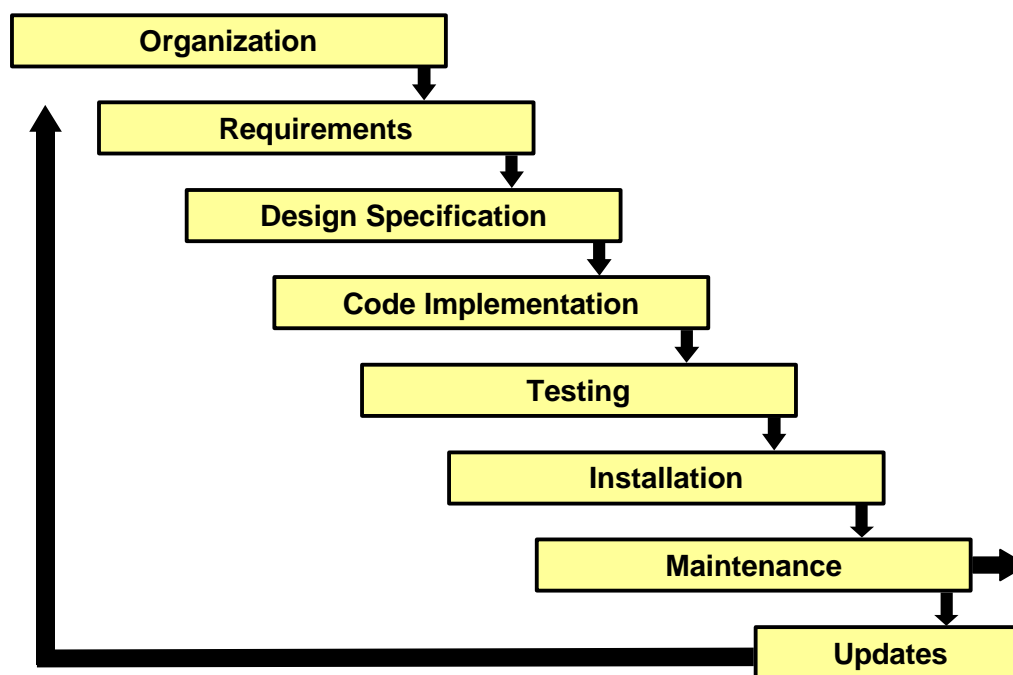


Figure 6. System Life-Cycle Development Steps

Table 3. Summary of System Life Cycle Documents

System Life Cycle Documentation	
Requirements	Describes what the system does.
Design Specifications	Provides detailed system architecture, logic, structure and performance specification.
Source Code	Provides the programming code with comments and illustrative diagrams.
Test Documents	Provides a compilation of test plans, test results and all verification steps.
System Installation	Provides software and hardware installation details. Describes supplied files and their configuration.
System Reference Manual	Describes the system usage including error messages and recovery procedures.
User Manuals and Tutorials	Provides an introductory and comprehensive description of how to use the system. Provides diagrams, screen shots, and examples in hardcopy and an on-line version. Self-paced tutorial guide.
Maintenance Procedures	Describes how to maintain and upgrade the system. Periodic test procedures, security, backup, and recovery procedures are described.
Change Control Procedures	Describes how to handle changes, revisions, updates and major additions. Identifies changes to current code and procedures as well as how to handle addition of models, modules, databases and other significant evolutionary changes.
Management	Describes ongoing system management and user control procedures.

Model validation determines how well the models are able to characterize hazard, exposure and risk compared to that occurring in the real world. CARES will allow the user to test the validity of lower tier (data poor) models by comparing their predictions to higher tier (data rich) models. As a result of this type of analysis, it is expected that data requirements will be further clarified. As a result of successive improvements in the models, it is expected that CARES will produce results that are accepted as an accurate and representative estimate of a specified population's distribution of exposure and risks.

A hallmark feature of the system will be its open source code available as electronic files, thereby allowing cooperative and independent evaluation and validation. CARES may be distributed under a license similar to the “copy-left” convention used by Linux (15).

5.0 User-Friendly Design

CARES will be a user-friendly, user-oriented program. User needs will be taken into account throughout the development process. CARES will take advantage of the last decade of research and technical advances in human-computer interface design to produce a high-quality, Windows-based, graphical interface that will appeal to both novice and advanced users alike. Good interface design is aimed at increasing the user’s ease of learning and mastery of the program, productivity, control over the system’s capabilities, and the accuracy and usefulness of outputs. A few examples of the underlying principles that serve to guide the user-friendly design of the system are:

- **Conventional** – reduces the learning curve by conforming to standardized Windows-based conventions (menus, buttons, tool bars, objects, etc.).
- **Consistent** – provides consistent use throughout the program for such elements as layouts, color use, action sequences, menus, prompts, help screens.
- **Easy** – minimizes learning and memory requirements through clear organization, on-screen guidance, intuitive design, easy access to help. Maintain ease of use as user proficiency increases by providing macro facilities, keyboard shortcuts, special menus.
- **Feedback** – provides informative and useful response to user actions. In addition to message responses, feedback includes appropriate changes in the visual display in response to user manipulation of objects and elements.
- **Error control** – allows repetitive undoing of actions, minimizes keyboard entry, provides internal safeguards coupled to user actions, and provides clear and constructive feedback and guidance to resolve user errors.

Version control will be maintained through distribution of electronic files to users. Additional materials will be provided to cover user instructional, reference, and information needs.

Descriptions of the type of materials to be provided include:

Source Code – provided as a series of text files.

Executable Code – compiled from the source code for a standard combination of hardware and operating system. For example, the CARES project will distribute the executable code compiled to run under Microsoft Windows NT on Intel Pentium II processors.

Demonstration CD – provide a general, multimedia overview and guided tour of the system features and functions.

Introductory Tutorial – includes “getting started” section for a quick introduction as well as a series of tutorials thoroughly covering all common features.

Advanced Tutorial – illustrating the use of more advanced features and describing more sophisticated or alternative uses of the system.

Online Interactive Tutorial – engaging the user in animated walkthroughs and interactive simulation of the system.

Quick Reference Guide – providing a summary of menu options and a concise overview of the syntax.

User Manual – detailed reference and information manual covering all aspects of the program features, operation, and underlying mathematical model.

Online User Manual – replica of the hard copy manual modified for hypertext use, glossary pop-ups, and searchable index.

Online Help – online help screen for each module with “F1” access to context-sensitive online help files containing hypertext contents, diagrams and screen shots, search facilities, and glossary.

System Life Cycle Documentation – series of development validation documents as described in Table 3.

Test Examples – used to verify the computational integrity of CARES when installed.



6.0 Glossary

BW – Body weight, usually in kilograms (kg).

Dose – The amount of a compound received by an individual, usually expressed as mg/kg BW and sometimes with the added dimension of time.

ED₁₀ – A statistical estimate of the dose which would cause an incremental effect of 10% in the exposed population, usually expressed as mg/kg BW/day. Also suggested for use as a “benchmark” dose in lieu of a NOAEL for calculating MOEs.

Exposure – The contact of a chemical with the surface of the human body (skin, lungs, and GI tract), usually expressed in terms of concentration and duration.

Hazard – The adverse effects or toxicity.

HI – Hazard Index. The sum of each exposure divided by its RfD.

MOE – Margin of Exposure. The benchmark dose (NOAEL or ED₁₀) divided by the dose from exposure. Also known as “margin of safety” (MOS).

NOAEL – No Observed Adverse Effect Level. The dose that caused no observable adverse effects in a toxicity study, usually expressed as mg/kg BW/day.

RfD – Reference Dose. The benchmark dose (often the NOAEL) divided by uncertainty factors.

Risk – The likelihood of adverse effects, usually expressed as an MOE, fraction of RfD, the HI, or a probability.

TEF – Toxicity Equivalency Factor. When products have a common mechanism of toxicity, it may be possible to normalize the dosage of each product to that of a reference product. For example, if 10 mg/kg BW/day of Chemical A produces the same effects as 1 mg/kg BW/day of the reference chemical. The TEF applied to Chemical A would be 0.1-fold.

UF – Uncertainty Factors. Default factors used to quantify uncertainty. Usually a 10-fold factor for intraspecies sensitivity, 10-fold for interspecies extrapolation, 10-fold for sensitivity of developing and juvenile animals, 3-fold for lack of a NOAEL in a study, and 1 to 1,000-fold for severity of toxic effects.

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