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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

Codex COMMITTEE ON PESTICIDE RESIDUES

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THE PROBABILISTIC APPROACH TO ACUTE DIETARY EXPOSURE ANALYSIS AND ITS APPLICABILITY AT THE INTERNATIONAL LEVEL (ANNEX)

(Transmitted by the United States of America)

EXECUTIVE SUMMARY

Pesticides are regulated in the U.S. under both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetics Act (FFDCA). In 1996, Congress passed the Food Quality Protection Act (FQPA) which amended both FIFRA and FFDCA and required that aggregate and cumulative risks be considered by EPA in granting pesticide tolerance petitions and in assessing whether pesticides can be reregistered for use. Through these statutes, EPA evaluates risks posed by the use of each pesticide to make a determination of safety. Only if the Agency determines that such residues would be "safe," may it authorize a tolerance to allow a pesticide residue in food.

Over the last several years, OPP has been working to expand its capability of evaluating acute dietary exposure and risk using probabilistic techniques of assessment. Currently, OPP is using probabilistic techniques (generally Monte-Carlo) to perform its exposure analyses. The Monte Carlo technique provides a relatively new tool in exposure assessment for more accurately estimating the complete distribution of exposures, and provides probabilistic and statistical assessment of dietary risk using more refined information than was used previously.

In 2001, CCPR requested that OPP describe its current probabilistic techniques and propose potential methods that could be implemented by CCPR in order to better evaluate exposure and risks of pesticides to the population. The current document was developed to provide details on the U.S. approach to probabilistic methods and attempt to suggest for consideration by CCPR methodologies that may be applicable for international level risk and exposure assessments. The purpose of this paper is to describe the overall framework and the general principles of the OPP's current probabilistic techniques for exposure assessment, to describe the current (deterministic) Codex exposure assessment procedures and their advantages and disadvantages, and discuss various potential approaches and possible "next steps" which might be considered in implementing the beginnings of any probabilistic methodologies.

Section I of this document describes the U.S. regulatory background of pesticide exposure assessment, provides a description of some of the science policy issues which will play a necessary and decisive role in implementation of any technical probabilistic procedures, and gives a brief introduction to the scope and organization of the document.

Section II of the document provides introductory background material on probabilistic exposure assessment as conducted in U.S. EPA's Office of Pesticide Programs[1]. OPP is using the DEEM (Dietary Exposure Evaluation Model) software in its probabilistic risk

[1]We recognize that probabilistic assessments of pesticide exposure are also performed by other nations (e.g., Canada, the United Kingdom, and the Netherlands) in support of regulatory decisions. These may vary in methodologies, inputs, interpretation, and policies. At this time to enable the meeting to focus on the methodology we have chosen to limit the scope of this paper to probabilistic methods as practiced in U.S. EPA's OPP.

assessment analyses for pesticides. With DEEM and it Monte-Carlo techniques, the entire distribution of exposures (across the U.S. population or any desired subgroup) can be evaluated instead of just an ill-defined “high-end” individual as is done with traditional deterministic techniques. OPP probabilistic techniques with DEEM software allow a more realistic evaluation of exposures and can consider the fact that not all crops are treated with a given pesticide and that a sizeable fraction of foods contains no pesticide residues at all. Rather than the crude "high-end," single point estimates generated earlier using deterministic techniques, DEEM software and Monte Carlo techniques provide more accurate information on the range and probability of possible exposure and their associated risk values.

Section III provides a brief description of the Codex’s current exposure assessment technique (the IESTI (International Estimate of Short-Term (Dietary) Intake procedure) and discusses some of its advantages and disadvantages. Current CODEX methodologies do not use probabilistic techniques in their assessment of human exposure to pesticides, but instead rely on point (or deterministic) estimates. This is based, in part, on an overall lack of extensive or detailed information concerning worldwide dietary/consumption patterns and pesticide residue concentrations in agricultural commodities. Thus, current Codex methodology involves estimation of a “high-end” exposure by means of the IESTI equation. The IESTI procedure currently used by Codex has a number of advantages. It is direct and relatively straightforward, requires minimal resources and data, and is reasonably intuitive. The primary advantages of the IESTI procedure–namely its simplicity, its ease of use, and its lack of need for extensive, additional data on either consumption or residue–are also its primary shortcomings. The IESTI formula does not take into account or consider a variety of factors which are of very real interest to a risk manager in making public health regulatory decisions. These additional factors can include likelihood of treatment, the range of actual application rates and pre-harvest intervals, the extent and rate of post-harvest degradation of the pesticide parent, and the fact that simultaneous exposure through other treated commodities can occur. In addition, an important (but well recognized) consequence of the IESTI procedure is that the assessment does not take a holistic (or “whole-truth”) approach to risk. Specifically, it can produce misleading results that can potentially misdirect risk mitigation efforts and activities. These considerations can be of critical importance in arriving at ostensibly rational public health decisions. Furthermore, the method can potentially mislead the risk manager with respect to appropriate public health decisions and mitigation measures.

Section IV of the document discusses some specifics associated with current databases available to Codex for assessments and offers some recommendations for methodologies for performing exposure assessments with minimal data. The above issues and limitations suggest a variety of methods which could be used to improve actual dietary exposures and initiate a first cut at development of at least rudimentary probabilistic methods. One possible methodology discussed in this section involves use of possibility theory, fuzzy arithmetic or probability bounds analysis. These techniques allow a risk analyst to obtain fully rigorous results with minimal input data and are

considered to be intermediate between a fully probabilistic assessment and a worst-case assessment relying on upper bound point estimates.

There are four appendices to this Annex. The first is a glossary that provides a series of useful definitions appropriate for probabilistic assessments. The second (Appendix 2) is entitled *"Probabilistic Risk Assessment and Monte-Carlo Methods: A Brief Introduction*" provides a simplified introduction to the topic, explaining what Monte-Carlo methods are, how they are performed, and how results are interpreted. The third appendix to the paper provides a detailed (but very simplified) example of a probabilistic exposure estimate that moves through each step in the process illustrating the procedures involved. A sample DEEM output is provided. Finally, Appendix 4 includes a list of references and suggested readings.

It is believed that the methods described in this document, by building upon and refining the current non-probabilistic CODEX procedures for estimating dietary exposure to pesticide, will substantially improve its ability to realistically evaluate the potential dietary exposure of individuals and the population to pesticides and thereby contribute to the goal of protection of public health.

I. Introduction

A. Overview

To determine whether food is safe to consume, regulators must assess the potential exposures from pesticide residues in food. To evaluate safety, they must use available and reliable, representative data. Such data includes information on a variety of factors including the toxicity of the pesticide (how much harm, if any, is caused by specific amounts of the pesticide) and the magnitude of the exposure to the pesticide. Exposure to a pesticide in the food supply depends, in turn, on two factors: the amount of the pesticide present in food and how much food a person eats.

Over the last several years, regulatory agencies have been working to expand their capability of evaluating acute dietary exposure and risk using probabilistic techniques of assessment.

Currently, U.S. EPA is using probabilistic techniques (generally Monte-Carlo) to perform its acute exposure analyses for food[2]. In these analyses, the entire distribution of exposures (across the U.S. population or any desired subgroup) can be evaluated instead of just an upper-bound point estimate taken to represent an ill-defined "high-end" individual used in traditional deterministic techniques. Probabilistic techniques allow a more realistic evaluation of exposures and can consider the fact that not all crops are treated with a given pesticide and that a sizeable fraction of foods contains no pesticide residues at all.

B. Scope and Organization of Document

The 2001 CCPR requested that certain governments describe their current probabilistic techniques and propose potential methods which could be implemented by CCPR in order to better evaluate exposure and risks of pesticides to the population. The current document was developed to provide details on present knowledge about probabilistic methods and to suggest for consideration by CCPR methodologies that may be applicable for international level risk and exposure assessments. As described in Section III of this paper, the current methodology used by Codex (the IESTI procedure) is quite clear, easily implemented and requires minimal data. While any probabilistic methodology introduced will no doubt involve considerably more complicated procedures and necessitate additional standard operating procedures and science policies on the part of Codex, we believe that these more advanced

[2]Although at present these probabilistic techniques are being used routinely in OPP only as applied to exposures through food, probabilistic techniques are applicable to a panoply of exposure pathways and risk scenarios. Drinking water and residential exposure assessments are two additional areas which OPP is currently investigating the use of probabilistic techniques.

methods can considerably improve the risk assessment process and lead to improved risk management decisions.

As is discussed in more detail in this introduction and later in the document, this paper describes the overall framework and the general principles of U.S. EPA's current probabilistic techniques for exposure assessment, briefly describes the current (deterministic) Codex exposure assessment procedures and their advantages and disadvantages, and discusses various potential approaches and possible "next steps" which might be considered in implementing the beginnings of any probabilistic methodologies.

Since the approaches discussed in the document are intended to apply only to the *methodological* aspects of the risk assessment process, it is important to note that the approaches discussed herein do not support or prescribe the use of any one particular confidence level, percentile, or percentage associated with regulatory acceptance. Thus, although the document may discuss in an exemplary manner a "99.9^{th} percentile" exposure estimate as US EPA's threshold of regulation for an acute probabilistic assessment, the decision to regulate at this percentile is a decision that was specific to the U.S.–implicit in which was the full consideration of the amount and quality of data (on both the exposure and toxicological side) available in the United States. Given the data available in other regions of the world concerning food consumption and pesticide residues, a decision to regulate at the threshold currently used by OPP (i.e., 99.9^{th} percentile) may not be appropriate in those regions: the availability and reliability of data concerning consumption and residue concentrations can and should have significant impact on any decision concerning the percentile at which to regulate.

This document is organized to present an overview of probabilistic methodologies that are used in estimating exposures from pesticides by some governments and to present possible approaches that Codex may want to consider in developing their techniques for acute exposure assessment at the international level. The paper does not attempt to present detailed information or calculations related to "risk" which is a function of both exposure and hazard. It is believed that such an integrated treatment would necessitate the inclusion and description of a variety of value-laden and science-policy judgments regarding safety and uncertainty factors and intra- and inter-species extrapolation factors. This is a complex topic that would merit an entirely separate, and quite detailed, discussion and cannot be appropriately considered within the scope of this paper. The current section (Section I) describes the U.S. regulatory background of pesticide exposure assessment, provides a description of some of the science policy issues which will play a necessary and decisive role in implementation of any technical probabilistic procedures, and gives a brief introduction to the scope and organization of the document. The document then, in Section II, provides introductory background material on probabilistic exposure assessment in the Office of Pesticide Programs. Section III provides a brief description of the

Codex's current exposure assessment technique (the IESTI procedure) and discusses some of its advantages and disadvantages. The next section (Section IV) discusses some specifics associated with current databases available to Codex for assessments and offers some recommendations for methodologies for performing exposure assessments with minimal data. There are four appendices in this Annex. The first is a glossary that provides a series of useful definitions appropriate for probabilistic assessments. The second (Appendix 2) is entitled *"Probabilistic Risk Assessment and Monte-Carlo Methods: A Brief Introduction*" provides a simplified introduction to the topic, explaining what Monte-Carlo methods are, how they are performed, and how results are interpreted. The third appendix to the paper provides a detailed (but very simplified) example of a probabilistic exposure estimate that moves through each step in the process illustrating the procedures involved. A sample Dietary Exposure Evaluation Model (DEEM™) output is provided. Finally, Appendix 4 includes a list of references and suggested readings. It is believed that the methods described in this document, by building upon and refining the current non-probabilistic Codex procedures for estimating dietary exposure to pesticide, will substantially improve its ability to realistically evaluate the potential dietary exposure of individuals and the population to pesticides and thereby contribute to the goal of protection of public health.

II. Probabilistic Exposure Assessment – Background Information

A. Information Sources for Estimating Human Dietary Exposure to Pesticides

Dietary food exposure estimate is derived from two distinct pieces of information:

- The amount of pesticide residue that is present in and on food (i.e., the residue level) and
- The types and amounts of food in consumer's diets (i.e., food consumption).

The residue information comes mainly from the crop field trials submitted by pesticide manufacturers and other sources or from monitoring data. Consumption information comes primarily from surveys of what people eat.

1. Food Consumption: Survey of Food Intake by Individuals

In the United States, the primary source of food consumption data used in dietary risk assessments is USDA's Continuing Survey of Food Intakes by Individuals (CSFII). The CSFII is particularly well suited to the

conduct of national level dietary risk assessments because it is statistically designed to sample individuals of all ages and ethnicities to accurately reflect national demographics. It is also balanced so that all seasons of the year and regions of the country are represented. The food survey data being used in the United States exposure and risk assessments are collected by the USDA in their 1994-96 CSFII combined with their 1998 Supplemental Children's Survey. Together, these surveys are referred to as the 1994-96/1998 CSFII. The 1994-96 CSFII, conducted as three separate 1-year surveys in 1994, 1995 and 1996, was designed to measure what Americans eat and drink. The 1998 survey (the Children's Supplemental Survey) was designed to be combined with and supplement the 1994-96 survey and concentrated on children aged from birth to 9 years old. It greatly expanded the number of children, increasing the number of survey participants in many smaller sub-age categories by four or five-fold. The table below presents the number of individuals who reported two (complete)-days of consumption data in the 1994-96/1998 CSFII (the number of person-days of intake available would be twice the numbers provided here):

Age Bin	No. Individuals
0 year old	1151 non nursing, 1408 total
1 year olds	1084
2 year olds	1107
3 year olds	1836
4 year olds	1859
5-6 year olds	1483
7-12 year olds	1589
13-19 year olds	1281
20+ year olds	9866

The USDA conducted personal in-home interviews in which interviewers ask individuals to recall everything they ate and drank over the previous 24 hours. Two (non-consecutive) days of food and nutrient intake data were collected. Subject to the cautions about statistical treatment of data, the data collected for such large numbers of survey participants, who have been scientifically selected so that results could be projected from the sample to the U.S. population, constitute a reliable and representative national sample.

In the Netherlands, The Dutch National Food Consumption Survey (DNFCS) has been carried out three times until now, with a five years period interval. The most recent survey of food consumption data is of 1997/1998. In this survey 6,250 respondents aged 1 to 97 years (of which 530 young children, aged 1 to 6 years) recorded their food intake over two consecutive days. The amount eaten was recorded accurately. The

respondents in the survey come from a representative sample of Dutch-speaking households as they occur throughout the country and the timing of the recorded days is distributed equally over the 7 days of the week and over the whole year (holidays excluded). For each individual age, sex, body weight and other relevant (a.o. socio-economic) characteristics are recorded. The unit of intake for the calculations of exposure to acutely toxic pesticides is 24 h in order to include random daily consumption patterns. Therefore from this food consumption data base 12,500 eating 'moments' are available for the total Dutch population and 1,060 moments for young children for use in Monte Carlo acute intake calculations. The same data base has been used to derive a set of Dutch large portion weight data for point estimates of acute exposure (which also has been sent to WHO for their international collection of large portion weight data).

The DNFCS does not include children below 1 year of age; therefore additional studies have been carried out to fill this gap. Next to the National Food Consumption Survey the RIKILT Wageningen UR has recently finalised a food consumption survey for 250 Dutch infants. A similar study has been done in Spain.

Additional food consumption survey information is available for the *United Kingdom.* These include the following surveys:

- The 1983 Schoolchildren study that surveyed ca. 3370 schoolchildren aged 10/11 and 14/15 and obtained estimates of consumption over 7 days. The study was limited to schoolchildren attending public schools where school meals were provided. The weights of schoolchildren were not provided and there was over sampling of Scottish children (age 10/11) and of children from lower socio-economic status families.

- The 1986 Infants Survey covered 488 infants from six to twelve months of age. Weights of the subjects were not recorded and one-parent families and ethnic minorities were underrepresented.

- The 1986/87 British Adults Survey was also a seven-day study of ca. 2200 adults between the ages of 16 and 65 living in private households. Body weights were recorded, but pregnant women and persons living in institutions were not included.

- The "British Adults Survey" performed by the UK's MAFF and the Department of Health (National Dietary and Nutrition Survey). The program is being performed as four separate surveys at intervals of approximately 2 years and focusing on the following four age groups: Children 1 ½ to 4 ½ years old, schoolchildren aged 5-15 years old, adults aged 16-64 years old, and adults aged 65 years old and older.

Many European countries do have good or reasonable food consumption surveys which In future will allow enlarging the number of European respondents on food consumption data bases, although they often have not been used and are not optimised for food safety issues in general and pesticide risk assessment in particular. A recent inventory of currently available European individual food consumption surveys has been published by Verger et al. (2002) in Eur. J. Clin. Nutr., supplement May 2002.

2. Residue Data Sources: Field Trials, Monitoring, and Market Basket Surveys

Data on the residues of pesticides in foods are obtained from a variety of sources. Traditionally, the primary source of residue data in foods has been field trial data that must be submitted in support of the registration of a pesticide. Crop field trials are experimental trials, usually performed by a pesticide manufacturer or other parties, in which the most extreme usage scenario (with respect to application rates, number of applications, pre-harvest intervals, etc.) is simulated. They are designed to determine maximum residues that may be present in fruit, vegetable, grain and other food and feed crops at the earliest point where these food commodities could enter commerce. These data are used to establish legally enforceable pesticide residue limits. These data over-estimate the residues that are likely to occur in food as actually consumed because they reflect the maximum application rate and shortest pre-harvest interval and do not account for residue degradation that sometimes occurs during the interval from the farm to the market to the home.

Data that are more reflective of residues on foods as consumed are often available from monitoring data in which food samples are obtained closer to the dinner table in the chain of commerce. In the U.S., these data come from surveys such as the Pesticide Data Program (PDP) conducted by the USDA, and Food and Drug Administration (FDA) Surveillance Monitoring data. These data generally provide a better characterization of pesticide residues in or on foods as purchased by the U.S. population.

Monitoring data are preferred over field residue trial residue data for use in assessing exposure to pesticide residues in food because they more closely simulate what is consumed. In the U.S., PDP pesticide monitoring activities are a federal-state partnership, whereby 10 participating states, which represent about 50 percent of the nation's population and all regions of the country, collect samples of fruit, vegetables, and other commodities. These samples are collected close to the point of consumption–at terminal markets and large chain store distribution centers immediately prior to distribution to supermarkets and

grocery stores. Such sampling therefore accounts for pesticide residue degradation during transit and storage, and provides data on residues resulting from postharvest applications of fungicides and growth regulators used as preservatives during food delivery. Samples are randomly chosen without regard for commodity origin or crop variety. In any typical year, approximately 600 samples of each of almost two dozen different commodities are analyzed for more than 100 pesticides and their associated metabolites. Generally, sampling occurs on any given commodity for at least two consecutive years before the commodity is "rotated out" of the program to be replaced by an alternate commodity. The commodities selected represent food that is typically available to the consumer for purchase throughout the year to provide the best available realistic estimate of exposure to pesticide residues in foods.

B. Acute vs. Chronic Assessments

Dietary exposure assessment can consider different exposure timeframes. Commonly, regulators use short term or "acute" exposures and long-term or "chronic" exposures; each assessment is calculated differently. In chronic exposure assessment, the risk assessor is attempting to estimate a person's *average* dietary exposure over the long-term (e.g., several months to a lifetime). Consequently, the use of both average (or arithmetic mean) residue value for each food commodity and average (or arithmetic mean) consumption of food commodities is regarded as appropriate. For acute exposure, regulators are instead interested in the amount that might be ingested on a single day; the mean exposure over a longer time period is insufficiently detailed to assess acute risk. To estimate acute dietary exposure, U.S. EPA uses a probabilistic exposure modeling technique called "Monte Carlo analysis."[3]

Older methods for acute dietary risk assessments for pesticide residues in foods assumed that 100% of a given crop with registered uses of a pesticide had been treated with pesticide and that all such treated crop items contained pesticide residues at the maximum legal level. The resulting acute risk estimates were considered "high-end" or "bounding" estimates and did not provide information on the variability and uncertainty nor any indication of how probable such high-end exposures were or what might be more expected exposure levels.

C. Acute Probabilistic (Monte Carlo) Techniques

One technique for estimating dietary exposure adopted by governments has been the Dietary Exposure Evaluation Model (DEEM™) computer software program. Unlike the previous software that was unable to properly incorporate

[3]For the purpose of discussion, this paper will use the term "Monte Carlo" keeping in mind that other probabilistic techniques may be used as well. This probabilistic assessment technique estimates the different levels of exposure people experience as the result of differences in the types and amount of foods they eat, as well as variations in the level of pesticide residue that may be present, among other factors.

the percent of a crop that was treated into its exposure evaluation and assumed only a single, high-end residue value in foods, DEEM™ can generate probabilistic assessments of acute dietary food exposure (i.e., can generate a distribution of one-day exposures across a population). Such probabilistic analysis is in contrast to deterministic analysis**,** where only a single, high-end residue value (*e.g.*, tolerance levels on foods) or perhaps a median value is used. DEEM™ uses a mathematical technique called Monte Carlo analysis to generate estimates of the *distribution* of pesticide dietary exposures by using all the individual food consumption and pesticide residue level data points included in a data set to determine the combined (or joint) distribution of exposures (and associated risk).

The Monte Carlo technique provides a relatively new tool in exposure assessment for more accurately estimating the complete distribution of exposures, and provides probabilistic and statistical assessment of dietary risk using more refined information than was used previously. This analysis uses the actual distribution of pesticide residue levels from either the experimental field trials or other monitoring surveys. Also, it can incorporate information on the percentage of the crop that is treated. That is, it includes the actual distribution of possible consumption and residue values and weighs these possible values by their *probability* of occurrence. Using Monte Carlo, it is not necessary to assume (as many prior procedures require) that 100% of the crops with registered uses are treated with the pesticide of interest or that all residues are present in crops at a single level (i.e., maximum legal levels). Monte Carlo instead provides more accurate information on the range and probability of possible exposure and allows assessment of the associated risk values.

It is important to note that Monte Carlo techniques are, in and of themselves, neither more conservative nor less conservative than any deterministic (or point-estimate) technique. Conservatism is determined, in part, by the risk manager when he or she determines the appropriate percentile of the model's output distribution (e.g., 99.9th percentile) to be used for regulation based, presumably in part, on the nature of inputs selected and assumptions used, and in part on science and regulatory policy. Monte Carlo and probabilistic techniques are simply tools that allow the risk assessor and manager to see a more accurate distribution of exposures among the general population and subpopulations, and any "decision threshold" for safety still rests upon the risk manager. The significant attribute of probabilistic techniques is that the information *used* by the risk manager is truer to the real world situation. And it is this broader, more realistic view of actual "real-world" exposure levels that makes these probabilistic methods so valuable in the risk assessment and risk mitigation arenas.

D. Adjustment of Input Parameters

It is possible to incorporate adjustments to a variety of input parameters in the Monte Carlo procedure using the DEEM™ software. U.S. EPA believes that

these adjustments result in a better estimate of true exposures. These adjustments are detailed in a variety of U.S. EPA Science Policy documents (see Reference List) and include use of information relating to percent crop treated and use of processing factors. Other adjustments to residue files include "decompositing" (more aptly termed "mathematical deconvolution") and use of ½ the analytical limit of detection for treating analytical results where no residue was detected (LOD) using the available analytical method.[4] Each of these adjustments is described in detail below.

1. Percent Crop Treated

The percentage of a given crop that is treated (or, more precisely, not treated) is a critical parameter for more refined (probabilistic) human health exposure assessments. This factor determines the proportion of crop that is assumed to have zero residues in the residue definition. It is important to recognize that Monte-Carlo assessments for acute exposures do not "adjust" the measured residue concentrations by the percent of the crop that is treated, but rather incorporate this information as the *probability* of encountering a residue in any individual's daily food consumption.[5] The probability of encountering a residue is done by incorporating true zeroes (reflecting untreated crop) into the residue distribution file used by the Monte-Carlo analysis in a proportion appropriate to simulate the probability of consuming an untreated commodity. A comparison of an invalid method and a valid method for incorporating %CT in an acute assessment is illustrated in the diagram below:

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[4] "Bridging" studies, "Residue Decline" studies," and "Residue Degradation" studies are additional studies that can be performed in an attempt to "adjust" residue values obtained from supervised field trials to more appropriately reflect the concentrations to which persons are actually exposed. Technically, these are not "factors" that are used in DEEM™, but rather adjustments to residue values that are used outside of DEEM™ in an attempt to make residues measured in supervised field trials more closely reflect real-world residues. These are discussed in the section entitled "Lack of Data regarding Pesticide Residue Values in Foods "As Consumed"" in Part IV of this paper.

[5] This contrasts with chronic assessments in which an individual is, over the long-term, exposed to an *average* (or arithmetic mean) residue value for which it IS appropriate to adjust a pesticide residue value by the percent of time it occurs (i.e., the percent of the crop which is treated)

Illustration of Valid and Invalid Means of Incorporating Percent Crop Treated (%CT) into an Acute Probabilistic Assessment	
Invalid	**Valid**
Residue Values ~~%CT~~ Resulting Residue 0.34 ppm 0.034 ppm 0.26 ppm 0.026 ppm 0.49 ppm } 10% 0.049 ppm 0.86 ppm 0.086 ppm 0.43 ppm 0.043 ppm	90% probability "0" (Zero) 10% probability 0.34 0.26 0.49 0.86 0.43

The method used to incorporate percent crop treated data is most appropriate when the same percentage applies across the entire population under evaluation. This is expected to be almost invariably true for many commonly consumed items such as canned fruit, canned and frozen vegetables, bottled juices or sauces, or cereal grains in almost any form.

This consideration may be closely analogous to current Codex concerns regarding differing agricultural and pest management practices between countries and how these differing practices may affect the risk picture on a local or smaller national scale versus an international assessment. Further study of whether and how to use percent crop treated data at the international level is warranted.

2. Processing Factors

The incorporation of processing factors into dietary exposure assessments can be routinely used to make the results more reflective of actual exposures. Specifically, commercial processing of agricultural commodities can increase or decrease concentrations of pesticides residues in foods: the magnitude and direction of this change is dependent upon the specific agricultural commodity, the nature and physical-chemical properties of the pesticide, and the characteristics of the processing procedure. Often, pesticide registrants are required to conduct commercial processing studies on certain foods to measure this impact on exposure, and these studies can be available for use at the international level. In cases where processing studies are not available, standard mass

balance assumptions can be used based on general information of the effects of some processing operations, such as drying of grapes to make raisins.

For other commodities that are not consumed without processing, and where data support the inclusion of a specific processing factor (either reduction or concentration), DEEM™ allows inclusion of the value into the residue data file. The residue measured in the raw commodity is multiplied by the processing factor prior to considering consumption of the processed commodity. If it is demonstrated, for example, that the canning of peaches results in a hundred-fold reduction in residues of a given pesticide, then a processing factor of 0.01 will be entered into the DEEM™ software and used to adjust the raw peach residue values present in a residue data file by this factor whenever consumption of "peaches, canned" is consumed. U.S. EPA also uses a default worst-case processing factor[6] when pesticide-specific data are not available.[7] These default factors are listed in Residue Chemistry Test Guidelines OPPTS 860.1520 Processed Food/Feed.

3. Decompositing

"Decompositing" is a mathematical procedure whereby measured residues in composite (or "bulk") samples are projected to represent residues in single items. This is needed in acute exposure assessments since it is not pesticide concentrations in composited samples that are of interest, but rather pesticide concentrations in the single items that an individual consumes that are needed. Composite sample analysis will provide an estimate of an *average* (mean) residue in that sample, but will not define residue concentrations in individual items within that composite. It is likely that individual items may have residue levels that are greater than the average. Therefore, a mathematical procedure is invoked in certain situations to "adjust" bulk or composite residue measurements to a single-item estimate.

These adjustments are necessary, however, only when it is believed that composite residue measurements could significantly underestimate residues in single items. This is particularly relevant when monitoring data (i.e., grocery warehouse sampling) are used for the residue input, since the composite samples collected at this point already

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[6] An exception, of course, would be when market basket or PDP data on the specific processed commodity (such as canned peaches) is available. In that case, the market basket data would be used.

[7] For example processing of tomatoes into tomatoes paste is considered a substantial change in form so a default processing factor (in this case, 5.5) is used when the registrant chooses not to perform this study or provide this information. Other processes (e.g, canning of green beans) are not considered to considerably alter the intrinsic nature of a commodity and no processing factor (or a processing factor of 1) is used.

incorporate a number of residue reducing factors. This decomposition procedure is analogous to Codex's use of a "variability factor" in that it attempts to adjust bulk residue measurements to account for consumption of single items.

It is believed by U.S. EPA that the composite sample measurements made in properly-conducted field trials in which maximum application rates and minimum pre-harvest intervals are observed provide an adequately conservative estimate of pesticide residues in single-items, so that in these instances, it is not necessary to decomposite the results. We note that this contrasts with the current IESTI procedure whereby a variability factor is introduced in order to adjust a residue measurement on a composite sample to reflect a single-item measurement even when those data arise from worst-case field residue trials.

Additional information regarding the U.S. EPA procedures for "decompositing" residue data is available in the document entitled "Use of the Pesticide Data Program (PDP) Data in Acute Dietary Assessment;" May 5, 1999, and available on the web at (http://www.epa.gov/fedrgstr/EPA-PEST/1999/May/Day-26/o-p13034.htm).

4. Use of Non-detect Values

In field trial residue data, the occurrence of samples in which no pesticide residue was detected requires a decision about how to include a precise quantitative value into the residue data file to be used for probabilistic analysis. Unlike non-treated crops, it can be assumed that there is a finite residue present, but that it is merely below the limit of determination. US EPA has chosen to use a value of ½ of the detection limit as a reasonable means to address such findings. This is clearly distinguished from consideration of non-treated crops (above) in which pesticide residue is properly assigned as "zero." Additional information concerning EPA's procedures for refining risk assessments and incorporating non-detects is available in the document entitled "Assigning Values to Non-Detected/Non-Quantified Pesticide Residues" (see http://www.epa.gov/fedrgstr/EPA-PEST/2000/March/Day-31/p7889.htm).

III. Current Codex Methodologies

Current Codex methodologies do not use probabilistic techniques in their assessment of human exposure to pesticides, but instead rely on point (or deterministic) estimates. This is based, in part, on a lack of available detailed information concerning worldwide dietary/consumption patterns and pesticide residue concentrations in agricultural commodities close to the point of consumption. Thus, current Codex methodology involves estimation of a "high-end" exposure by means of the IESTI

(International Estimate of Short-Term (Dietary) Intake) equations. The basic equation (case 2a) is shown on the following page[8]:

$$\mathbf{IESTI = \{[U \times RL_P \times V] + [\max(0, LP - U) \times RL_P]\} \div bw}$$

where:

U	=	the median unit weight of the commodity unit (kg)
RL_P	=	the highest residue level reported on a composite sample incorporating processing or edible Portion factors (mg/kg)
V	=	variability factor
Max		is the function indicating that the maximum of either zero or the value produced by subtracting the weight of one commodity unit (U) from the large portion consumption weight (LP) is used. In other words, if the commodity unit weight exceeds the large portion consumption weight, then zero is used in the second term of the numerator.
LP	=	the large portion consumption data for the commodity (97.5 percentile) (kg)
bw	=	the mean body weight for the target population subgroup (kg)
IESTI	=	International Estimated Short -Term Intake

The IESTI formula estimates a "high-end" pesticide intake from a single commodity by assuming that the first unit consumed contains a residue concentration equal to the highest value obtained in a field trial and that all subsequent units contain residue concentrations equal to the highest (composite) value of the composites of the field trial residues[9]. The residue value in the "first" unit consumed (e.g., a pear) is adjusted by a "variability factor" to account for the fact that field trial residue measurements are performed on *composite* samples and any single unit (e.g., a single pear) could contain higher residue values (higher by a factor of up to V) than were observed in the composite. It is further assumed that the total amount consumed of this commodity by an individual is equal to the 97.5th percentile consumption on an "eaters only" basis. An example calculation is shown in the box on the following page:

[8] Variations of the IESTI equation are used. Where the concentration in a composite sample reflects that in a meal-sized portion (U < 25g), the equation is IESTI = (RL_P X LP) ÷ bw [case 1]. Where LP >U [case 2b], LP is substituted for U in the equation of case 2a [above]. Where a commodity is blended or bulked [case 3], the STMR or STMR-P is substituted for the RL_P, and LP is substituted for U in the equation of case 2a [above]. Report 2001.

[9] IESTI has also considered using a median value of all field trials performed for the crop of interest. Use of a high value simulates the situation in which the supply available to an individual for consumption is derived from a single lot. As can be seen in the IESTI formula, this high value is NOT adjusted by the variability factor since it represents a composite sample, the residue of which is assumed to be relevant to consumption of all subsequent commodities (i.e., after the first) on that day.

The following is a sample IESTI calculation using the residue data used in the illustrative example calculation in Appendix 3

Potato

IESTI = {[0.160 kg x 10 mg/kg x 7] + [0.279 kg – 0.160 kg] * 10 mg/kg} / 14.5 kg bw
= 0.854 mg/kg bw

Peach

IESTI = {[0.099 kg x 6 mg/kg x 7] + [0.316 kg – 0.099 kg] * 6 mg/kg} / 19 kg bw
= 0.287 mg/kg bw

Note to the reader: the IESTI procedure calculates *separate* exposure estimates for potatoes and peaches assuming high-end residues and high-end consumption in each case. A comparable sample DEEM analysis is provided in Appendix 3 to this paper which demonstrates use of this same residue data using DEEM software and its Monte-Carlo procedures. As is explained in the Appendix, it is assumed that ca. 50% of each crop is treated but no processing or cooking factors are used or assumed to apply. As seen in this Appendix' 3's DEEM output, comparable exposure (eaters only) for this hypothetical data set for children 1-6 years old is estimated as 0.024 mg/kg, 0.048 mg/kg, and 0.089 mg/kg, at the 95th, 99th, and 99.9th percentiles, respectively. These estimates jointly consider potato and peach consumption and represent 12.0%, 24.1%, and 44.6% of the acute RfD, respectively (assuming that the acute RfD (or acute PAD) is 0.2 mg/kg/day). One can see that in the IESTI procedure, the IESTI-derived exposure estimates represent 430% of the acute RfD for potatoes alone (0.854 mg/kg/0.2 mg/kg) and 144% of the acute RfD for peaches alone (0.287 mg/kg/0.2 mg/kg). When the DEEM exposure estimates are represented on a per capita basis (i.e., eaters and non-eaters considered together), the percent RfDs occupied at the 95th, 99th, and 99.9th percentiles are 2.5%, 12.0% and 29.5%, respectively.

The IESTI procedure has a number of advantages. It is direct and relatively straightforward, requires minimal resources and data, and is reasonably intuitive. In addition, the formula can be modified, as appropriate, to consider processing factors. Importantly, the formula provides a "bounding" or worst-case estimate of potential dietary intake on an individual commodity basis and provides a risk assessor with a good idea of an intake from an individual commodity that is extremely unlikely to be exceeded.

However, the formula does not purport to represent the probabilities of these events occurring, nor does it purport to estimate a full range of dietary intakes, or the effect on total pesticide intake of consuming additional (other) commodities that contain residues (all subsequently consumed commodities are assumed to be free of pesticide residues). This is due, in part, to difficulties in making "universal" assumptions that would apply equally well to the different regions, climates, and agricultural practices that affect pesticide residues levels and to the various dietary customs and preferences of the peoples of the world that affect consumption. The formula also includes a number of implicit and explicit assumptions that tend to bias the intake estimate. Importantly, some of the assumptions bias the intake estimate low and others bias it high. The net result of these biases is that it may be difficult to state overall whether IESTI-based

exposure estimates are under- or over-estimates of reality. Some of the assumptions include the following:

- Residues are considered to be present only in the specific commodity of interest and all remaining foods consumed during the day are assumed to be pesticide residue-free.

- Residues are present in the first item consumed at a value that represents an adjusted-maximum concentration found in supervised field trials. This adjustment factor is designed to correct the concentrations measured on a composite sample to the level that *would have been found* in a single-item.

- Residues are assumed present in all subsequently eaten items of the commodity of interest at a concentration equal to the highest composite residue concentration found in supervised field trials [case 2a].

- Residues are present in the agricultural commodity of interest at concentrations reflective of the most extreme GAP practices. No account is made for actual use rates or pre-harvest intervals or for subsequent degradation of residues following harvest in the channels of commerce or during storage. In reality, there is expected to be a large difference (generally one to two orders of magnitude or more) between residues found in field trials and those found closer to the dinner plate.

On the one hand, residues may be present in other consumed food commodities and accounting for this possibility is desirable to estimate total daily dietary intake of a pesticide (and not just intake from a single "high-end" residue food source). Ignoring other food sources of the same pesticide residue would tend to produce exposure estimates that are biased low. On the other hand, the adjustment of a measured residue in the highest composite sample from a supervised field trial (using most extreme GAP) to arrive at a hypothetical concentration in a single-item compounds conservatisms and tends toward a worst-case or "bounding" estimate. Although in the vast majority of instances, the combination of these procedures would be expected to overestimate dietary exposures, it cannot be taken *prima facie* that this occurs in all situations.

An important (but well recognized) consequence of the IESTI procedure is that the assessment does not take a holistic (or "whole-truth") approach to risk. Specifically, it can produce misleading results that can potentially misdirect risk mitigation efforts and activities. For example, it is conceivable that one pesticide (Pesticide A – a highly acutely toxic one) is present at high concentrations at the GAP-prescribed pre-harvest interval following foliar application but degrades very quickly during shipment and is easily washed off such that residues are essentially non-existent at the time it is purchased by the consumer. There may be another soil-applied pesticide (Pesticide B – slightly less toxic) that exists as an alternative to the first, but is more persistent (degrades very slowly), cannot be removed by washing, and is present in foods at the

time of consumption at concentrations essentially equivalent to those at harvest time. The IESTI procedure might result in a conclusion that Pesticide B is a "safer" pesticide since it is slightly less toxic and present at lower concentrations at harvest time. In reality, this might be an artifact of the risk assessment methodology: Pesticide A could be viewed as the "safer" pesticide since it degrades quickly and is not found in the commodity during transit or storage or in commercial or retail distribution channels. Because it relies on the supervised trial residue data, the IESTI procedure focuses on estimating a worst-case pesticide intake, not the intakes that are more reasonably anticipated at the time of purchase or consumption.

In general, then, the IESTI procedure can be considered to represent a theoretical "bounding" estimate of a pesticide intake through a single commodity. While it does represent a potential maximum intake by an individual consuming a treated commodity, it does not account for additional dietary exposures that may occur through other (treated) commodities. As such, it is impossible to definitively conclude whether the pesticide intake estimate as produced by the IESTI procedure is an overestimate or underestimate of actual "real world" exposures: while it is almost certainly an overestimate of exposure through a single commodity, it is not known whether it is also an overestimate of exposure through the multiple potentially- treated commodities which an individual consumes in a short period. Importantly, the more commodities which are treated, the more likely it is that the IESTI procedure underestimates total daily intake. To make reasonably realistic estimates of exposures through the multiple potentially-treated commodities which an individual may consume requires the use of probabilistic techniques. It is in this way that more accurate information on the range and probability of possible exposure and their associated risk values can be obtained and used in the assessment of risks and evaluation of potential mitigation options.

A brief example calculation comparing the IESTI procedure and standard IESTI inputs with a fully probabilistic (Monte-Carlo) procedure that uses inputs typical of those used by the U.S. EPA (i.e., USDA's PDP data) is considered here. This example uses real data for an insecticide to compare estimated exposures and risk to children 1-6 years old from two commodities -- grapes and spinach. The IESTI procedure estimates exposure from grapes and spinach using data from actual field trials that were submitted for this chemical. The probabilistic methodology used USDA PDP data for grapes and spinach in the manner that U.S. EPA would normally use it. The acute RfD for this particularly pesticide is assumed to be 0.02 mg/kg bw. This is done through the following equations for spinach and grapes:

Spinach

IESTI = {[0.100 kg x 5 mg/kg x 7] + [0.377 kg – 0.100 kg] * 5mg/kg} / 17kg bw
= 0.287 mg/kg bw

Grapes

IESTI = {[0.118 kg x 9.1 mg/kg x 7] + [0.286 kg – 0.118 kg] * 9.1 mg/kg} / 15.9 kg bw
= 0.569 mg/kg bw

Thus, the IESTI procedure would estimate that exposure represents 1,435% of the acute RfD for spinach alone (0.287 mg/kg/0.02 mg/kg) and 2,845% of the acute RfD for grapes alone (0.569 mg/kg/0.02 mg/kg). As noted previously, this procedure calculates *separate* exposure estimates for spinach and grapes assuming high-end residues and high-end consumption in each case. The body weight values are associated with the source nation for the LP (large portion).

A comparable sample DEEM™ analysis was performed, which demonstrates use of PDP data using DEEM™ software and its Monte-Carlo procedures. Specifically, PDP results from 1996 (spinach and grapes) and 1997 (spinach only) were used to represent concentrations to which consumers would be exposed. A total of 1027 samples are available over two years from this data source for fresh spinach (with 113 detects) and 525 samples for grapes (with 39 detects). Furthermore, information on percent crop treated was incorporated into this assessment: 43% was used for spinach and 17% was used for grapes. That is, the probabilistic procedure was performed in such a way that 83% (or 1- 17%) of the probabilistic "draws" for grapes and 57% (or 1- 43%) of the probabilistic "draws" for spinach resulted in selection of an untreated sample (i.e., are with zero residues). As seen in the DEEM™ output in Figure 1, comparable exposure (eaters only) for this real data set for children 1-6 years old is estimated as 0.0002 mg/kg, 0.0015 mg/kg, and 0.0080 mg/kg, at the 95th, 99th, and 99.9th percentiles, respectively. These estimates jointly consider spinach and grape consumption and represent 1.17%, 7.63%, and 40.1% of the acute RfD, respectively. When the DEEM™ exposure estimates are represented on a per capita basis (i.e., eaters and non-eaters considered together), the percent RfDs occupied at the 95th, 99th, and 99.9th percentiles are 0.00%, 0.66% and 9.99%, respectively[10]. In both cases, it can be seen that exposures estimated using the most realistic data along with probabilistic methodology result in substantially reduced estimates of exposure.

[10] Much of the difference between the estimates (at comparable percentiles) using "eaters only" and "eaters and non-eaters considered together" is due to the fact that only two commodities are considered in this example and thus (in the "eaters only" case) all individuals who did not consume at least one of the two commodities are excluded from the analysis and, thus, the %acute RfD occupied reflects only those individuals who consumed one or more of the commodities of interest. As additional commodities (or more commonly consumed commodities) are included in the assessment, the percent acute RfD occupied between the "eaters only" analysis and the "eaters and non-eaters" analysis are expected to converge. The U.S. considers the "eaters and non-eaters" in its assessment but will, if significant differences exist between this estimate and the "eaters only" estimate, note and consider the results of the "eaters only" assessment on a case-by-case basis.

Figure 1. Sample DEEM™ Output

```
U.S. Environmental Protection Agency                                  Ver. 7.74
DEEM ACUTE Analysis for X                                  (1994-98 data)
Residue file: chemicalx.RS7                  Adjustment factor #2 used.
Analysis Date: 10-23-2001/07:40:56
Residue file dated: 10-23-2001/07:15:51/8
Acute Reference Dose (aRfD) = 0.020000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 4000      MC list in residue file     MC seed = 25
================================================================
Children 1-6  yrs                 Daily Exposure Analysis
-----------------                 (mg/kg body-weight/day)
                                   per Capita    per User
                                  -----------  -----------
           Mean                      0.000010     0.000075
           Standard Deviation        0.000247     0.000677
           Percent of aRfD               0.05         0.37

       Percent of Person-Days that are User-Days = 13.15%


  Estimated percentile of user-days falling below calculated exposure
    in mg/kg body-wt/day with Percent of aRfD

 Percentile   Exposure     % aRfD          Percentile   Exposure     % aRfD
-----  ----------  ---------          ----------  ----------  --------
10.00      0.000000       0.00            90.00      0.000077     0.38
20.00      0.000000       0.00            95.00      0.000234     1.17
30.00      0.000000       0.00            97.50      0.000527     2.64
40.00      0.000000       0.00            99.00      0.001526     7.63
50.00      0.000000       0.00            99.50      0.002829    14.15
60.00      0.000000       0.00            99.75      0.004641    23.20
70.00      0.000000       0.00            99.90      0.008021    40.10
80.00      0.000003       0.02

Estimated percentile of per-capita days falling below calculated exposure in mg/kg
body-wt/day with Percent of aRfD

Percentile   Exposure     % aRfD       Percentile   Exposure     % aRfD
 ----------  ----------  ---------    ----------  ----------  ---------
    10.00      0.000000       0.00        90.00      0.000000     0.00
    20.00      0.000000       0.00        95.00      0.000000     0.00
    30.00      0.000000       0.00        97.50      0.000005     0.03
    40.00      0.000000       0.00        99.00      0.000133     0.66
    50.00      0.000000       0.00        99.50      0.000333     1.67
    60.00      0.000000       0.00        99.75      0.000735     3.67
    70.00      0.000000       0.00        99.90      0.001998     9.99
    80.00      0.000000       0.00
```

The comparisons above serve to illustrate differences in the risk assessments. The primary advantages of the IESTI procedure–namely its simplicity, its ease of use, and its lack of need for extensive, additional data on either consumption or residue–are also its primary shortcomings. The IESTI formula does not incorporate a variety of factors that are of crucial interest to a risk manager in making public health regulatory decisions. These additional factors can include likelihood of treatment, the range of actual application rates and pre-harvest intervals, the extent and rate of post-harvest degradation of the pesticide parent, and the fact that simultaneous exposure through other treated commodities can occur. These considerations can be of critical importance in arriving at ostensibly rational public health decisions. Furthermore, the method can potentially mislead the risk manager with respect to appropriate public health decisions and mitigation measures. As demonstrated earlier in the text, failing to consider that, in practice, a given pesticide decays rapidly following application or that a given pesticide is almost never applied as per the label maximums, may lead a decision-maker to mistakenly conclude that one pesticide poses less public health risk than another.

Probabilistic risk assessments should endeavor to incorporate all relevant and available information concerning the likelihood and magnitude of that risk and appropriately caveat any uncertainties. This includes incorporating the best information available in an attempt to capture the most realistic picture of true pesticide exposures across a population. To incorporate repeated compound conservatism on the one hand with biased simplifying assumptions on the other may result in a risk estimate which has little basis in reality and the characterization of which is meaningless. In fact, it is conceivable that risk-related decisions that are meant to be public health protective may in fact end up as being misleadingly anti-protective due to undue reliance on faulty assumptions and unrealistic scenarios. OPP recognizes that there may be specific, very unusual, or very localized issues that may lead to anomalous (but infrequent) higher exposures than exposures experienced by broader population groups. These specific circumstances can (and should) be separately considered and analyzed by the risk assessor and should not be allowed to grossly alter assessments in the name of conservatism; if probabilistic assessments are performed with the proverbial “thumb on the scale” then their likely utility to risk managers and decision-makers will be greatly diminished.

IV. Future Needs for International Probabilistic Risk Assessments

Currently CCPR is investigating the possibility of modifying its standard IESTI procedure to better account for available information and for the possibility of multiple exposures through consumption of more than one treated commodity in a day. The developments in the EU might serve as an example of the possibilities to use existing national data bases to come to a regional collection of food consumption data, which can be used for the implementation of the Monte Carlo method in an international approach. In fact, in 1998 and 1999, the Scientific Committee on Plants of the EU expressed an opinion on Monte Carlo methodology and proposed to use this technique

as much as possible in the evaluation of pesticide residues in the registration procedure. The methodology is being further studied and developed by several EU projects (and are mostly oriented on applying Monte Carlo calculations in connection with pesticide residue monitoring data). Within a period of one or two years Monte Carlo applications, including European consumption data, are expected to become available via Internet and will strongly enhance the accessibility of Monte Carlo simulations within Europe and worldwide. These applications will include relevant variables like variability of the residue, influence of processing, percentage crop treated etc. As a consequence of the foreseen risk management discussions, however, these variables may change to some extent and maybe new elements will have to be included.

Ideally, any selected methodology would use all available information to permit the risk manager to consider the range and likelihood of exposures across a population and do this using probabilistic techniques. Some of the main limitations to implementation of such techniques are:

- Lack of survey-based dietary consumption data for many regions of the world.

- For those countries that do have survey-based dietary consumption data, in many cases sample sizes are very small and there is concern about the ability to adequately predict high-end exposures with such small samples[11]

- Apart from the single-serving sampling program performed by the UK Ministry of Agriculture, Fisheries, and Food (MAFF) in 1993-96, the EU/Norway/Iceland Coordinated Monitoring Program begun in 1996, and the extensive monitoring done in the US by the FDA and USDA, there is essentially no standard widely available "beyond the field trial" data available that provides information on pesticide residues on food as consumed. The pesticide residues as determined and measured in supervised crop field trials are acknowledged to substantially overestimate residues in produce as consumed in the vast majority of cases.

- Lack of available or reliable national data on percent of crop treated; data on regional, national, or supra-national commodity distribution patterns; typical application practices with respect to rates and timing; and data on the effect of processing on residues.

Overall, then, the lack of adequate data on a variety of fronts results in a limitation on the ability to fully use probabilistic techniques in estimating exposures to pesticides through food at the international level. Each of these limitations is discussed, in turn, below along with background information and some thoughts for addressing these limitations.

[11] Note that there is also the corollary concern for the presence of outlier consumption values, or consumption values at the high-end which are not representative of the population as a whole.

A. Lack of Survey-Based Dietary Consumption Data for Many Regions of the World

There is a lack of survey-based dietary consumption data for many regions of the world. This issue has been and will likely remain a principal obstacle to any widespread and universal adoption and implementation of probabilistic exposure assessment techniques. Nevertheless, WHO/FAO is currently investigating the results of cluster-analysis of regional dietary differences (see "Consideration of Intake of Pesticide Residues: Report of the Joint FAO/WHO Expert Consultation on Food Consumption and Exposure Assessment") and this analysis may result in a greater understanding of dietary consumption in nations that have minimal data regarding food consumption. In any case, it seems that a tiered approach to these analyses might be appropriate in which at least a start at a probabilistic approach is considered in those countries that do have at least some survey-based data. As these methods progress and additional information is developed, it is possible that diets could be considered in a regional context which could permit broader use of the data and individual country data sets to be combined and used jointly in an attempt to create a more robust data file.

B. Small Sample Size for Consumption Survey Data

For those countries that do have survey-based dietary consumption data, in many cases sample sizes are small Naturally, sample size comparisons are not the only factor which should be considered in comparing survey procedures: such considerations as survey design, degree and extent of oversampling, homogeneity of eating patterns and practices, non response biases, etc. are important to consider as well. Moreover, sample size as a percentage of the total national population may be substantial. For example, the Dutch National Food Consumption Survey (DNFCS) contains only 530 in the group "Children 1-6 years old," but this is a significant portion of the total Dutch population (0.003% total population; 0.02% of Dutch children). The USDA CSFII 1994-96/1998 survey contained 7400 children, also 0.003% of the total population but only 0.012% of US children.

The food consumption survey sampling data that is available is limited and is missing substantial portions of important information. A significant concern with small surveys is that they may not adequately capture high-end consumption values that do in fact occur in the population. For example, it may be that the (true, but unknown) 99^{th} percentile consumption of orange juice is 12 g/kg/day, but with only a very limited number of survey participants, what is the probability of capturing something that high? Similarly, it may be that on only one day of 1000 [person-days of consumption] does an individual consume, for example, a ginkgo nut. How likely is it that a small survey will appropriately reflect this probability? Conversely, small surveys may give undue weight to "inappropriately captured" outliers that don't truly reflect consumption patterns of

the underlying population. It may so happen that of 1000 people surveyed, one individual reported consuming six apples in a day. Does this really reflect the 99.9+ percentile consumption for apples? Or is it just that the statistical survey loses its ability to discriminate and estimate at these high percentiles?[12] These are all issues that must be considered in reflecting on the reliability of any food consumption survey and that will limit the full use of such data. It may be possible to investigate this question by comparing (statistically and otherwise) national surveys to one another to note areas of similarities and differences. This would be particularly effective for those regions that have similar diets (as per, for example the WHO clustered regional diets analysis). This could be done with a variety of graphical plots (e.g. cumulative distribution plots, Q-Q plots etc) and a variety of statistical techniques. For example, one could compare apple juice consumption as estimated by one national survey with apple juice consumption as estimated by a second (different) national survey. If there aren't significant differences between surveys and if high-end consumption values appear to be adequately captured by (and appropriately reflected in) the smaller surveys, then it might be possible to combine these surveys or otherwise use them to assist in a quasi-validation of the smaller surveys and enhance our ability to use them fully.

In the longer term, it may be possible to expand national surveys (or perhaps perform larger, trans-national survey across the EU, for example, or in other FAO designated clusters) to obtain additional data. The availability of adequate consumption data in connection to their application in Monte Carlo calculations is also studied and promoted in EC-funded research: it may be advisable to focus such a study and place initial emphases regarding data collection, at least to start, on children 1-6 since these are often found in U.S. analyses to be a sentinel group, i.e., if the U.S. acute PAD is exceeded, it is frequently due to the exposure estimates associated with this specific group. This would have the advantage of permitting maximum use of any limited resources available for surveys and, in the majority of cases, could be expected to be protective of all other aged subpopulations. This is currently being addressed in a more limited age group by the EU in their effort to study and develop consumption data for infants, which until now are mostly lacking in consumption data bases. It is to be expected that within a few years it may be possible to overcome the problems of the difficult comparability of the various national consumption databases, so that it may be possible to construct a European consumption data base with which European Monte Carlo calculations can be performed.

C. Lack of Data regarding Pesticide Residue Values in Foods "As Consumed"

[12] Note that this is the corollary concern for the presence of outlier consumption values, or consumption values at the high-end which are not representative of the population as a whole.

Apart from the single-serving sampling program performed by the UK MAFF in the early to mid 1990's, the EU/Norway/Iceland Coordinated Monitoring Program initiated in 1996, and the extensive continual monitoring done in the US by the FDA and USDA, there is essentially no widely available international "beyond the field trial" data that provides extensive information concerning pesticide residues on food as consumed. The pesticide residues as determined and measured in supervised crop field trials are acknowledged to substantially overestimate residues in produce as consumed in the vast majority of cases. Thus, it might be considered advantageous to consider two levels of assessment – the first for when fairly extensive market- or consumer- level residue monitoring data is available for the conduct of a probabilistic risk assessment and a second level which could be used when such data is not available.

First Level: Pesticide residue monitoring data from the U.S. and Europe might be considered of sufficient intensity and duration to be used in a "first level" assessment – one in which a full probabilistic assessment could be performed. The U.S. EPA routinely uses USDA's PDP data as a component of its risk assessments. PDP is designed to provide information on pesticide residues in food in order to improve the quality of data that EPA uses to estimate exposure. The data collected under this program is ideal in many respects for use in a probabilistic exposure assessment for pesticides: samples are collected as close to the point of consumption as possible (while still retaining the identity of product origin) and sampling is based on statistically reliable protocols. Samples are apportioned according to each State's population and the commodities selected are chosen, in part, for their significance in the diet with specific emphasis on fruits and vegetables commonly consumed by children. In general, approximately 600 samples of each of about 20 commodities are collected under this program and analyzed annually for dozens of pesticides and their metabolites.

The EU has also initiated a coordinated monitoring program that similarly attempts to obtain extensive monitoring data for use in risk assessments. This EU/Norway/Iceland Coordinated Monitoring Program is, in many respects, similar to the U.S. PDP program that the U.S. EPA uses as a principal basis for many of its risk assessments for pesticides. A variety of EU states are participating in an EU- coordinated monitoring program. Several Council directives require Member States to report to the Commission the results of the monitoring program for pesticide residues carried out both under their national program and under the EU coordinated program. Those programs have existed since 1996. Their aim is to work towards a system that makes it possible to estimate actual dietary pesticide exposure throughout Europe. Specifically, sample collection under the EU program occurs from warehouses, central markets, importers, auctions, processors, and retailers and is under the purview of each national government. The monitoring program is designed as a rolling program, which will have covered all major pesticide-commodity combinations by the end of 2003. The choice of commodities includes the major components of the Standard European Diet of the World Health Organization. In 1997, the EU program sampled five

commodities: mandarins (tangerines), pears, bananas, beans, and potatoes. In 1998, sampling of oranges, peaches, carrots, and spinach was conducted. In 1999, samples of cauliflower, peppers, wheat, and melons occurred. In 2000 and 2001, sampling continued and is currently occurring in 2002. It is expected that the sampled commodities will compare favorably with the "Top Kids Foods" identified in the U.S. (see below) and might be expected to be large components of the diet in the EU nations:

Apple fruit	Egg	Potato, w/o peel
Apple juice	Grape	Rice
Apple sauce	Grape juice	Soybean oil
Banana	Milk fat	Sugar (sugarcane)
Beef	Milk non-fat solids	Tomato
Sugar (sugarbeet)	Oats	Tomato puree
Chicken	Orange	Wheat flour
Corn syrup	Orange juice	
Corn, sweet	Pork	

The data now or soon-to-be available under this EU sampling program should permit a good initial estimate of pesticide exposures using probabilistic techniques and would be useful in informing the EU of what additional commodity data is most in need.

Alternatively, or to supplement the EU Coordinated Monitoring Program, CCPR could attempt to make use of actual *existing* monitoring data from the U.S. PDP program, as well as the Netherlands, Japan, and the UK or any representative monitoring data in any quantitative Monte-Carlo assessments. Together, these data sources may provide a very robust data set with which to estimate distributions of exposure. Distributions of residue levels, by commodity, could be compared *across* countries. If there were little significant differences in residue levels in those commodities that are expected to contribute most significantly to risk, then this might provide added support for expansion of current national monitoring programs to a supra-national level.

Second Level: For those regions in which minimal or no extensive pesticide monitoring data is available for consideration in a probabilistic assessment or for those specific *commodities* for which such data is not available, a "second level" of assessment which is less refined than the first, but which requires substantially less data might be considered[13]. One option might be to attempt to relate concentrations observed during supervised field trials to concentrations that would be expected to be seen in channels of trade immediately prior to purchase and consumption. In general, the U.S. finds that concentrations found in produce

[13] This option would also be applicable for first registration purposes. In these situations, no monitoring will be available and 100% crop treated might be assumed at least as an initial preliminary estimate.

sampled by USDA's PDP program from warehouses and central distribution points immediately prior to shipment to supermarkets and grocery stores are approximately one to two orders of magnitude lower than concentrations generally observed in field trials. Although this has not been investigated quantitatively and is seen more as a "general rule of thumb", this is an area that could be investigated and possibly evaluated in a more quantitative manner. In addition, the UK's MAFF conducted a massive single-item monitoring program during the years 1993 to 1996 in an effort to relate composite to single-item residue concentrations, and this data could be used to obtain semi-quantitative estimates of factors to account for differences between residues as measured in field trials and those measured closer to the consumer. Regardless of whether it is determined to be appropriate to attempt to derive universal factors relating pesticide concentrations as measured in supervised field trials to pesticide concentrations observed in commercial channels, it appears that substantial benefit could be derived if effort were placed into deriving estimates of pesticide residues for at least the more commonly consumed items (particularly the more commonly consumed children's foods) which may have higher residue concentrations.

Another option would be to continue to use the pesticide measurements generated from supervised field trials, except to use the **entire distribution** in a probabilistic assessment (instead of just the maximum detected value and the median residue as is currently done with the IESTI formula). Currently, this is similar to the US approach which is used when PDP, FDA, or other monitoring data is not available or inadequate (e.g., frequently the case with a new chemical for which monitoring data is not available or appropriate). This is termed a "Tier 1" or "Tier 2" assessment when performed by US EPA. In these cases, 100% of the crop is assumed to be treated, either tolerance (for not blended or partially-blended commodities) or average (for blended commodities) field trial data are used, and the threshold of regulation is 95% (instead of 99.9% which is used when percent crop treated is incorporated). As a general rule of thumb, we have found that estimated exposures using a Tier 1 or Tier 2 assessment at the 95th percentile are about an order of magnitude greater than the same assessment when done in a manner which incorporates PDP or FDA monitoring data and uses actual estimates of percent crop treated (instead of assuming 100% treated). While this methodology is not considered an ideal approach (it uses biased residue data which are known to overestimate actual exposures at the consumer level), it is an approach than can be performed in many cases with the pesticide residue data from supervised field trials that is currently collected and available. A minor modification of this procedure would be to use bridging (or reduced-use) and residue decline data in that they permit the risk assessor to incorporate a range of residues resulting from various application rates or PHIs that are used in actual practice. The purpose of the bridging (reduced-use) field trials is to compare (or "bridge") the residues resulting from the maximum application rate to those representing typical rate(s). The purpose of the residue decline (and also the residue degradation) trials is to develop a relationship

between residue concentration and time. It is these "relationships" that are used to adjust the supervised field trial residues to account for the fact that not all applications are performed at the maximum label rates (in the case of bridging studies), that not all harvests performed at the minimum pre-harvest interval (in the case of residue decline studies), and that not all consumption occurs immediately following harvest (residue degradation studies). Additional information on these studies can be found in "Guidance for Refining Anticipated Residue Estimates For Use in Acute Dietary Probabilistic Risk Assessment" dated June 15, 2000 and available on the web at http://www.epa.gov/oppfead1/trac/science/#additional.

D. Lack of Available or Reliable National Data on Pesticide Application Patterns and Practices or on Commodity Distribution Patterns

There is frequently little data available on pesticide application patterns and practices or on commodity distribution patterns. Thus, it is difficult to estimate percent crop treated or, its corollary of interest, the probability of consuming a treated commodity. The U.S. performs its risk assessments using PDP data and assumes that a certain percentage of the crop is not treated and is therefore devoid of residues. It then uses this percentage to factor in a number of "true zeroes" into its assessment using these to replace the ½ LOD values that would normally be used (as described previously). Frequently, however, it is not the ½ LODs that contribute substantially to any risk. The U.S. has a policy whereby a sensitivity analysis is performed to determine if the use of zero vs. ½ LOD produces substantial changes in estimated high-end (e.g., 99.9th percentile) exposures. This would be something that could be done as a standard procedure in those instances where there is uncertainty about whether residues are 0 or residues are ½ LOD.

E. Other Probabilistic Techniques

The above issues and limitations suggest a variety of methods that could be used to improve actual dietary exposures and initiate a first cut at development of at least rudimentary probabilistic methods. One possible methodology involves use of possibility theory, fuzzy arithmetic or probability bounds analysis. Possibility theory has been offered as a way to quantify non-statistical forms of uncertainty and is based on weaker axioms involving fewer assumptions than its more well-known cousin "probability theory." Fuzzy arithmetic is a more robust subset of this theory with weaker sensitivity of the final results to the specific details regarding the shapes of the input.

We note that the EPA's OPP has no experience with this methodology and would therefore not be able to offer CCPR advice or guidance regarding its

implementation or conduct. It is considered to be on the “cutting edge” of probabilistic techniques and is being used in a variety of situations by other U.S. government agencies and by private consulting firms where minimal data is available.

APPENDICES

List of Appendices

APPENDIX 1

Appendix 1: Glossary

Beta Distribution is a flexible, bounded PDF described by two shape parameters. It is commonly used when a range of the random variable is known.

Boxplot is a graphical representation showing the center and spread of a distribution, along with a display of outliers.

Central Limit Theorem says that for a relatively large sample size, the random variable x (the mean of the samples) is normally distributed, regardless of the population's distribution.

Coefficient of Variation (also Coefficient of Variance or Coefficient of Variability)* is an estimate of relative standard deviation. Equals the standard deviation divided by the mean. Results can be represented in percentages for comparison purposes.

Confidence Interval is the range within which one has a given level of confidence that the range includes the true value of the unknown parameter (e.g., a 95% confidence interval for a parameter means that 95% of the time the true value of that parameter will be within the interval).

Continuous Probability Distribution* is a probability distribution that describes a set of uninterrupted values over a range. In contrast to the Discrete distribution, the Continuous distribution assumes there are an infinite number of possible values.

Correlation, Correlation Analysis is an investigation of the measure of statistical association among random variables based on samples. Widely used measures include the linear correlation coefficient (also called the product-moment correlation coefficient or Pearson correlation coefficient), and such non-parametric measures as Spearman rank-order correlation coefficient, and Kendall's tau. When the data are nonlinear, non-parametric correlation is generally considered to be more robust than linear correlation.

Correlation Coefficient* is a number between -1 and 1 that specifies mathematically the degree of positive or negative correlation between assumption cells. A correlation of 1 indicates a perfect positive correlation, minus 1 indicates a perfect negative correlation, and 0 indicates there is no correlation.

Cumulative Distribution Function (CDF) is alternatively referred to in the literature as the distribution function, cumulative frequency function, or the cumulative probability function. The cumulative distribution function, F(x), expresses the probability the random variable X assumes a value less than or equal to some value x, F(x)=Prob(X, x). For continuous random variables, the cumulative distribution function is obtained from the probability density function by integration. In the case of discrete random variables, it is obtained by summation.

Cumulative Frequency Distribution is a chart that shows the number or proportion (or percentage) of values less than or equal to a given amount.

Deterministic Model, as opposed to a stochastic model, is one which contains no random elements.

Discrete Probability Distribution* is a probability distribution that describes distinct values, usually integers, with no intermediate values. In contrast, the continuous distribution assumes there are an infinite number of possible values.

Distribution is the pattern of variation of a random variable.

Frequency (also Frequency Count)* is the number of times a value recurs in a group interval.

Frequency Distribution* is a chart that graphically summarizes a list of values by subdividing them into groups and displaying their frequency counts.

Goodness-of-Fit is a set of mathematical tests performed to find the best fit between a standard probability distribution and a data set.

Goodness-of-Fit Test is a formal way to verify that the chosen distribution is consistent with the sample data.

Group Interval is a subrange of a distribution that allows similar values to be grouped together and given a frequency count.

Histogram is a plot of the range of values of a variable into intervals and displays only the count of the observations that fall into each interval.

Interquartile Range is the difference between the third quartile (75th percentile) and the first quartile (25th percentile).

Kurtosis* is the measure of the degree of peakedness and flatness of a curve. The higher the kurtosis, the closer the points of the curve lie to the mode of the curve. A normal distribution curve has a kurtosis of 3.

Lognormal Distribution is the distribution of a variable whose logarithm is normally distributed.

Mean is the arithmetic average of a set of numerical observations: the sum of the observations divided by the number of observations

Measurement Error is error introduced through imperfections in measurement techniques or equipment.

Median is the value midway (in terms of order) between the smallest possible value and the largest possible value. It is that value above which and below which half the population lies

Mode* is that value which, if it exists, occurs most often in a data set.

Monte Carlo Analysis (Monte Carlo Simulation) is a computer-based method of analysis developed in the 1940's that uses statistical sampling techniques in obtaining a probabilistic approximation to the solution of a mathematical equation or model. It is a method of calculating the probability of an event using values, randomly selected from sets of data repeating the process many times, and deriving the probability from the distributions of the aggregated data.

Non-parametric Approach is one that does not depend for its validity upon the data being drawn from a specific distribution, such as the normal or lognormal; a distribution-free technique.

Normal Distribution is a probability distribution for a set of variable data represented by a bell shaped curve symmetrical about the mean.

OPP is the Office of Pesticide Programs in the Office of Prevention, Pesticides, and Toxic Substances of the United States Environmental Protection Agency.

Parameter. Two distinct, but often confusing, definitions for parameter are used. In the first usage (preferred), parameters refers to the constants characterizing the probability density function or cumulative distribution function of a random variable. For example, if the random variable W is known to be normally distributed with mean μ and standard deviation □, the characterizing constants μ and □ are called parameters. In the second usage, parameters are defined as the constants and independent variables which define a mathematical equation or model. For example, in the equation Z=X+Y, the independent variables (X,Y) and the constants (,) are all parameters.

Parametric Approach is a method of probabilistic analysis in which defined analytic probability distributions are used to represent the random variables, and mathematical techniques (e.g., calculus) are used to get the resultant distribution for a function of these random variables.

Percentile is the value that exceeds X percent of the observations.

Population is the total collection of observations that is of interest.

Probability (Classical Theory) is the likelihood of an event.

Probabilistic Approach is an approach which uses a group of possible values for each variable to estimate risk.

Probabilistic Model is a system whose output is a distribution of possible values.

Probability Density Function (PDF) is a distribution of values for a random variable, each value having a specific probability of occurrence. It is alternatively referred to in the literature as the probability function or the frequency function. For continuous random variables, that is, the random variables which can assume any value within some defined range (either finite or infinite), the probability density function of a point expresses the probability that the random variable falls within some very small interval; the PDF at a point multiplied by the width of a very small interval containing the point approximates the probability that the random variable falls within that interval. For discrete random variables, that is, random variables which can only assume certain isolated or fixed values, the term probability mass function (PMF) is preferred over the term probability density function. PMF expresses the probability that the random variable takes on a specific value.

Quantile-Quantile (Q-Q) Plot portrays the quantiles (percentiles divided by 100) of the sample data against the quantiles of another data set or theoretical distribution (e.g., normal distribution). By comparing the data to a theoretical distribution with a straight line, departures from the distribution are more easily perceived.

Random Error is error caused by making inferences from a limited database.

Random Number Generator* is a method implemented in a computer program that is capable of producing a series of independent, random numbers.

Random Variable is a quantity which can take on any number of values but whose exact value cannot be known before a direct observation is made. For example, the outcome of the toss of a pair of dice is a random variable, as is the height or weight of a person selected at random from the New York City phone book.

Range* is the difference between the largest and smallest values in a data set. Alternatively, it expresses the interval between the minimum and maximum values (i.e., (min x_i, max x_i))

Regression Analysis (Simple) is the derivation of an equation which can be used to estimate the unknown value of one variable on the basis of the known value of the other variable.

Sampling. One of two sampling schemes are generally employed: simple random sampling or Latin Hypercube sampling. Latin hypercube sampling may be viewed as a stratified sampling scheme designed to ensure that the upper or lower ends of the distributions used in the analysis are well represented. Latin hypercube sampling is considered to be more efficient than simple random sampling, that is, it requires fewer simulations to produce the same level of precision. Latin hypercube sampling is generally recommended over simple random sampling when the model is complex or when time and resource constraints are an issue.

Sensitivity Analysis is an analysis that attempts to provide a ranking of the model's input parameters with respect to their contribution to model output variability or uncertainty. In broader sense, sensitivity can refer to how conclusions may change if models, data, or assessment assumptions are changed.

The difficulty of a sensitivity analysis increases when the underlying model is nonlinear, nonmonotonic or when the input parameters range over several orders of magnitude.

Simple Random Sampling (SRS) is a sampling procedure by which each possible member of the population is equally likely to be the one selected.

Simulation, in the context of Monte Carlo analysis, is the process of approximating the output of a model through repetitive random application of a model.

Skewness is the measure of the degree of deviation of a curve from the norm of a symmetric distribution. The greater the degree of skewness, the more points of a curve lie to one side of the peak of the curve. A normal distribution curve having no skewness is symmetrical, that is to say that there exists a central value a such that f(x-a)=f(a-x), f(x) being the frequency function.

Standard Deviation is a measure of dispersion which is expressed in the same units as the measurements. It is a measurement of the variability of a distribution, i.e., the dispersion of values around the mean. Standard deviation is the square root of the variance for a distribution .

Standard Error of the Mean is the standard deviation of the distribution of possible sample means. This statistic gives one indication of how precise the simulation is.

Stochastic is a term referring to a process involving a random variable.

Triangular Distribution is a distribution with a triangular shape. It is characterized by its minimum, maximum and mode (most likely) values. It is often used to represent a truncated log-normal or normal distribution if there is little information available on the parameter being modeled.

Variability refers to observed differences attributable to true heterogeneity or diversity in a population or exposure parameter which cannot be reduced by additional data collection.

Sources of variability are the result of natural random processes and stem from environmental, lifestyle , and genetic differences among humans. Examples include human physiological variation (e.g., natural variation in bodyweight, height, breathing rates, drinking water intake rates), weather variability, variation in soil types and differences in contaminant concentrations in the environment. Variability is usually not reducible by further measurement or study (but can be better characterized).

Variance is a measure of the dispersion, or spread, of a set of values about a mean. Variance is the square of the standard deviation, i.e., the average of the squares of the deviations of a number of observations from their mean value. When values are close to the mean, the variance is small. When values are widely scattered about the mean, the variance is larger.

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APPENDIX 2

Appendix 2: Probabilistic Risk Assessments and Monte-Carlo Methods: A Brief Introduction

Risk assessments are a crucial part of EPA's pesticide regulatory program and have been for over 25 years. These assessments are used to estimate impacts on human health and the environment from the use of a given pesticide. Agency policy is that risk assessment should be conducted in a tiered approach, proceeding from simple to more complex analyses as the risk management situation requires. The Agency has traditionally used "deterministic" assessments involving point estimates of specific parameters to generate a single estimate of exposure and risk based on various assumptions about the concentration of pesticide in any given medium (e.g., food, water, air etc) and the amount of that medium consumed, breathed, or otherwise contacted. Deterministic assessments can begin with worst-case assumptions (for example, residues on foods at tolerance levels), then can be refined by more realistic values that remain point estimates (for example, average residues from field trials). Even with a tiered approach, each deterministic assessment provides single values for estimates of exposure from a given pathway. Such single-value risk estimates do not provide information on the variability and uncertainty that may be associated with an estimate.

Current Agency Policy (5/15/97) is that *probabilistic* analysis techniques (of which Monte-Carlo is one example) can be viable statistical tools for analyzing variability and uncertainty in risk assessments, provided they are supported by adequate data and credible assumptions. Probabilistic techniques can enhance risk estimates by more fully incorporating available information concerning the *range* of possible values that an input variable could take, and weight these values by their *probability* of occurrence. As an example, a particular food commodity (e.g., tomatoes) might contain a range of pesticide residues for any given pesticide, with a large percentage of tomatoes consumed actually containing no residues at all (since not all tomatoes are treated). In addition, individuals may or may not consume tomatoes on any given day and, over time, are expected to consume varying amounts of this food item due to varying daily consumption patterns. Probabilistic risk analysis permits OPP to assess the range of exposures (and their associated probabilities) that result from combinations of the various residue levels and consumption patterns. The resulting output of a probabilistic determination is a distribution of risk values with probability assigned to each estimated risk. Some of the major differences between deterministic and probabilistic estimates are summarized in the table below:

Deterministic Risk Assessment	Probabilistic Risk Assessment
□ Pesticide concentrations and potential exposure factors are expressed as point estimates. □ The risk estimate is also expressed as point value. The variability and uncertainty of this value are not reflected.	□ Takes into account all available information and considers the *probability* of an occurrence. □ The risk estimate is expressed as a distribution of values, with a probability assigned to each value. □ The distribution reflects variability and uncertainty.

Tiered Approach to Risk Assessment

As risk assessments are refined, assumptions can proceed from more conservative (more health protective) to more realistic reflections of exposure. As noted above with the example of residues on food, such refinements can be applied to deterministic assessments. Probabilistic analyses, including Monte Carlo, represent numerical techniques to reflect more realistic assumptions. For example, Tier I of acute dietary assessments as conducted by OPP includes conservative assumptions such as: all foods consumed by an individual in any given day were treated with the pesticide in question (if registered for use on that food) and that residues are present in those consumed foods at the maximum legal limit. Monte-Carlo techniques fully applied to this situation would allow incorporation of information concerning the percent of the crop that is treated, the amount of pesticide applied and timing of its application, and the range and distribution of residue values expected to be found. This information is useful because a

particular food (e.g., tomatoes) might contain a range of pesticide residues for any given pesticide, with a large percentage of tomatoes consumed actually containing no residues at all (since not all tomatoes are treated). In addition, individuals may or may not consume tomatoes on any given day and, over time, are expected to consume varying amounts of this food item due to varying daily consumption patterns. Any variability and uncertainty is explicitly included in the analysis and is fully disclosed.

The Origin of Monte-Carlo Techniques

Monte-Carlo techniques have been used since the 1940's when they were first developed by physicists working on the Manhattan project. Only recently, however, have personal computers become sufficiently powerful and widespread for Monte-Carlo techniques to be widely applied for health risk assessments. Modern spreadsheet programs now provide a range of critical facilities to help to illustrate and order a model including advanced statistical functions, charting, etc. And the simplicity and capabilities of recently introduced commercial Monte-Carlo software allows these techniques to become virtually all but routine.

The origin of the name “Monte-Carlo” relates to the famous gambling city in Monaco, but the relation to gambling applies only to the probability of a given event occurring over the long term. Although one cannot know precisely which number will appear on the next roll of a craps die or the spin of a roulette wheel, one can predict over the long term (and as precisely as desired) the frequencies associated with each outcome. Monte-Carlo numerical techniques similarly cannot predict exactly which exposures will occur on any given day to any specific individual, but can predict the range of potential exposures in a large population and each exposure’s associated probability.

What is Monte-Carlo Analysis?

Monte-Carlo analysis is simply one of several mathematical techniques for performing probabilistic risk assessments. The Monte Carlo technique, as applied to exposure assessment, involves combining the results of hundreds or thousands of random samplings of values from input probability distributions in such a manner as to produce an output distribution that reflects the expected range and frequency of exposures. Although computationally-intensive, Monte-Carlo techniques themselves are not complicated. Assessing a Monte-Carlo analysis requires examining the appropriateness of assumptions, judgments, and data sets that are key inputs to the mathematical procedures.

The first step in a Monte-Carlo simulation is the construction of a model that accurately represents the problem at hand. The makeup of the model usually entails a mathematical combination (addition, multiplication, logarithms, etc.) of the model input variables that can be expressed as probability distributions. If, for example, one desires to simulate the daily dietary pesticide exposure to individuals from a particular pesticide in tomatoes, this can be simulated by repeatedly drawing random values from two separate distributions: one distribution represents tomato consumption by individuals while the other represents pesticide levels in tomatoes. Here, the output variable (daily pesticide exposure) is defined as the product of the two input variables (tomato consumption in grams/day and pesticide residue concentrations in µg/g). Each random pair of input variables obtained from repeated independent samplings of the input distribution are multiplied together and the product used as one point in the distribution for the output variable. In general, this process is repeated thousands of times and the thousands of output products generated, taken together, form a distribution of frequencies. This technique is more fully illustrated in the box on the following page:

Suppose that our two input variables are defined as a and B where a = {2, 4, 6, 8, 10}, B = {10, 20, 30, 40, 50}, and our output variable C is defined as the product of a and B (i.e., C = a x B). Set a might represent the concentration of a pesticide in tomatoes (in µg/g) and Set B might represent the daily consumption of tomatoes (in g/day). We wish to determine the range and frequency of potential values of C (which in this case would represent daily exposure to the pesticide in µg/day). Inspection of the input data immediately reveals that the value for C (daily exposure) can range from a low of 20 µg/day (i.e., 2 x 10) to a high of 500 µg/day (i.e., 10 x 50) and that each of these two extreme values should occur approximately 4% of the time (i.e., 1/5 x 1/5 = 1/25 = 4%), Monte-Carlo methods permit us to evaluate **all** values that can be generated for the value C along with each of their associated probabilities. The Monte-Carlo method randomly chooses a single pesticide concentration value from Set A and a single tomato consumption value from Set B. These two values are multiplied together (to give daily pesticide exposure, C) and this resultant value stored. This process is repeated thousands of times with all values of C eventually plotted as a frequency histogram as shown above. Note that the lowest value is 20 µg/day and the highest value is 500 µg/day, just as originally predicted. Note also that these two values each occur approximately 4% of the time, just as (again) predicted from our original inspection. Although this example uses discrete values for sets a and B, Monte-Carlo modeling can also be performed when the input variable are described as continuous variables.

Regardless of how accurately the fitted distribution conforms to the data, or what method of sampling is used, the analyst has to set up a model that reflects the situation being assessed. According to Vose's *Quantitative Risk Analysis: A Guide to Monte Carlo Simulation Modeling*, the cardinal rule of risk analysis modeling is: "Every iteration of a risk analysis model must represent a scenario that could physically occur." Following this rule will lead to a model that is both accurate and realistic. As an example, it would be improper to model a cow diet as a random sampling of feeds with established tolerance for the pesticide of interest since many of the diets generated in such a manner would be unreasonable with respect to the roughage/nonroughage components, carbohydrate/protein mix, commodity combinations, and economic constraints. In short, blind application of Monte-Carlo techniques without regard for the reality of the generated scenarios will produce absurd results with no basis in reality. The analyst should ensure that each of the hundreds or thousands of iterations is a scenario with real-world possibilities.

It is often tempting in risk analysis modeling to include very unlikely events that would have a very large impact should they occur. A rare event of concern is defined as an event that has a low probability of occurrence but a potentially high impact on the results of a risk analysis. The expected impact of a rare event is determined by two factors: the probability that it will occur and the distribution of possible impacts. For example, widespread systematic illegal use of a pesticide or gross calibration errors in a pesticide's application might be a situation that occurs to some unknown (but relatively insignificant) extent. Since the probabilities of these events are so difficult to quantify, their determination provides a stumbling block for the analyst. However, since it is impossible to cover all scenarios that might exist and to calculate the probability of such occurrence, including the rare event in the general model will not increase our understanding of reality and will limit the clarity of the model.

Random Nature of the Monte Carlo Analysis

Integral to any Monte-Carlo analysis is the generation of random numbers. Similar to rolling dice, the software has a 'random number generator' that produces a random sequence of numbers. Two main forms of sampling are Random Sampling (also called Monte Carlo Sampling) and Latin Hypercube sampling. Random or Monte Carlo sampling will evaluate the probability distributions in a purely random fashion, and is useful in trying to get the model to imitate a random sampling from a population or for doing statistical experiments. However, the randomness of this sampling suggests that, unless a very large number of iterations are performed, it will over-sample some parts and under-sample other parts of the distributions. Because for nearly all risk analysis modeling exploration of the distribution extremes (the "tails") is important, exact reproduction of the contributing distributions of the model becomes essential.

Latin Hypercube sampling (LHS) addresses this issue by providing a sampling method that appears random but that also guarantees to reproduce the input distribution with much greater efficiency that the random sampling. LHS uses a technique known as stratified sampling without replacement. It breaks the probability distribution into 'n' intervals of equal probability, where 'n' is the number of iterations to be performed on the model. Then, at random, one sample is drawn from each section, forcing, this way, an equal-chance representation of all the portions of the distribution. The Latin Hypercube method leads to a predictable uniformity of the sampling of the distribution.

For More Information

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APPENDIX 3

EXAMPLE CALCULATIONS

DEEM™ EXPOSURE ANALYSIS
(FOOD ALONE)

Appendix 3: Example Calculations

NOTE TO READER

These example calculations are provided to give a basic understanding of how a Monte Carlo analysis might be conducted for exposures through food using a software system which operates like DEEM™. The level of detail provided is such that non-specialists should be able to better understand the basic components of, and ideas behind, the dietary risk assessments performed by OPP. To understand the specific details regarding any actual assessment, it is necessary to carefully review the inputs and assumptions that underlie that specific assessment. These details are provided with each assessment when it is released. To understand the details of the DEEM™ software program, which is used to generate these assessments, it is necessary to examine the operation and structure of the software in some detail. While this appendix refers to the operating algorithms of DEEM™, OPP does not required that any specific software be used. DEEM™ and Lifeline™ (another dietary exposure analysis software program) have both gone to the FIFRA Scientific Advisory Panel (SAP) for review, and the details of how they operate, including critical portions of their computer codes, are publicly available and can be accessed through the web. CARES (Cumulative and Aggregate Risk Evaluation System), another exposure software currently in development by Crop Life America, is scheduled to be presented to the SAP in April.

Monte Carlo Analysis

Monte Carlo analysis is one of several mathematical techniques for performing probabilistic assessments. The method relies on the computational powers of modern computers to simulate the range and frequency of all possible outcomes of a process based on repeatedly sampling from the inputs provided by the user. These inputs are combined according to the model that is specified by the user. Thus, for example, to assess the entire range of possible food exposures to pesticides, and their probability of occurrence, would require:

(1) specification of a model that combines food consumption and pesticide residues on that food; and

(2) provision of input values for residues and consumption.

Once the computer software is provided with the necessary inputs, it will generate the output as a distribution of all possible exposures by repeatedly sampling from the inputs and combining these inputs according to the model. Whether this output distribution is an appropriate representation of the distribution of exposures in the real world depends on: (1) the relevance of the model, by which the inputs are combined, to the actual processes in the real world, and (2) the accuracy, or representativeness, of the inputs into the model.

For each step discussed below, the critical pieces of the Monte Carlo analysis--the input files and the model used to combine the inputs--will be examined in some detail. Following this, an example will be provided showing how these input files may be combined using the model specified for that type of assessment.

DEEM^{TM} is the software that the Agency routinely uses in its food risk assessments. There are two major inputs into the food exposure assessment: 1) files on what food is eaten by which individuals and in what quantity; and 2) files on pesticide residues estimated to be on that food. The consumption files contain information on exactly what each individual ate as well as demographic and other ancillary information (e.g., age, sex, weight) on each individual. This data file is "hardwired" in the DEEM^{TM} software–that is, it cannot be changed by the user. This is because this file simply reports the exact information provided by the USDA Continuing Survey of Food Intakes by Individuals (CSFII) food consumption survey. The other data file, that contains the pesticide residues, is a "soft" file--that is, it contains information expected to be input by the user, and would likely change for each assessment. Estimates of resulting exposure (which represents the combining of data on food consumed with pesticide concentrations in those foods) are generated on a general U.S. population and specific sub-populations (e.g., children) bases using the demographic and other information available for each individual in the CSFII survey. In addition, self-reported body weight is used to convert exposure in mg of pesticide/day into mg of pesticide/kg of body weight/day, so that it can be compared to a toxicological endpoint expressed in mg pesticide/kg body weight/day. This is because toxic doses are expressed on a standardized basis (per kg/body weight) and not simply as an absolute amount (simply as an absolute amount as in "mg pesticide").

Inputs

Food exposure estimates are derived from two distinct pieces of information:

1. the amount of pesticide residue that is present in and on food (i.e., the residue level) and

2. the types and amounts of food in a person's diet (i.e., food consumption).

The residue information comes mainly from chemical specific monitoring data collected by the USDA and FDA or, when these are not available, from the crop field trials submitted by pesticide manufacturers and USDA. The OP cumulative assessment will rely heavily on available monitoring data. Consumption information comes primarily from USDA surveys of what people eat. These input data are described in detail below.

(1) Food Consumption: USDA Continuing Survey of Food Intake by Individuals

The primary source of food consumption data used in dietary risk assessments is the Continuing Survey of Food Intakes by Individuals (CSFII). The CSFII is particularly well suited for national- level dietary risk assessments because it is statistically designed to sample individuals of all ages and ethnicities to accurately reflect national demographics. It is also balanced so that all seasons of the year and the major regions of the country are represented.

The food survey data being used in the OP cumulative exposure and risk assessments were collected by the U.S. Department of Agriculture in the 1994-96 surveys and the 1998 Supplemental Children's Survey. Together, these surveys are referred to as the 1994-96/1998 CSFII.

The 1994-96 CSFII was conducted as three separate one-year surveys in 1994, 1995 and 1996. The 1998 survey (the Children's Supplemental Survey) was designed to be combined with and supplement the1994-96 survey. It concentrated on children aged from birth to nine years old. The supplemental survey greatly expanded the number of children included in the survey, increasing the number of survey participants in many sub-age categories by four- or five-fold.

USDA has been conducting these food surveys since the 1930s by means of personal interviews in which interviewers ask individuals to recall everything they ate and drank over the previous 24 hours. Specifically, the CSFII (1994-96/1998) data are derived from information provided by thousands of individuals who participated in the survey. In this most recent survey, two (non-consecutive) days of food and nutrient intake data for individuals of all ages were collected by personal in-home interviews. The data collected for such large numbers of survey participants, who have been scientifically selected so that results could be projected from the sample to the U.S. population, constitute a reliable and representative national sample.

(2) Residue Data Sources: Monitoring, Market Basket Surveys, and Field Trials

Data on the residues of pesticides in foods are obtained from several sources. These include USDA's Pesticide Data Program (PDP), the FDA Total Diet Study, and (sometimes) various pesticide registrant-sponsored market basket surveys. Data from USDA's **Pesticide Data Program** are EPA's principal source of monitoring data for use in assessing risk from exposure to pesticide residues in food. Additional information about this survey is provided below:

- PDP pesticide monitoring activities are a federal-state partnership. Ten participating states, which represent about 50 percent of the nation's population and all regions of the country, collect samples of fruits, vegetables, and other commodities.

- PDP's statistically-reliable sampling protocol is designed to select random samples that best represent pesticide residues in the food supply to allow for a realistic estimate of exposure. The sampling protocol was developed in cooperation with the Agency and the data generated are specifically designed to be used for risk assessment. Fresh agricultural products and processed foods are widely distributed, therefore, it is assumed that each person has the same probability of being exposed to any given residue.

- Samples are collected close to the point of consumption–at terminal markets and large chain store distribution centers immediately prior to distribution to supermarkets and grocery stores. They take into account pesticide degradation during transit and storage, and provide data on residues resulting from post-harvest applications of fungicides and growth regulators.

- The number of samples collected is apportioned according to state population or commodity turnover information.

- Samples are randomly chosen without regard for commodity origin or variety. They reflect what is typically available to the U.S. consumer throughout the year.

Another source of information used in the OP cumulative risk assessment is FDA's **Total Diet Study**. This is a monitoring program, conducted by the U.S. Food and Drug Administration, in which pesticide residues are determined in foods prepared as if for consumption. Samples are collected four times a year (one time in each of the four U.S. Census regions of the U.S.). A sample consists of foods purchased in three cities within a given region. In total, 240 different foods are sampled and the database, taken together, provides information concerning pesticide exposures over time.

Additional data for risk assessments are sometimes available in the form of the **Market Basket Surveys**. In these studies, pesticide registrants sometimes join together in a consortium to develop residue data for use in pesticide risk assessments. Some specifics regarding these surveys are provided below:

- In these studies, samples are generally obtained from grocery stores and supermarkets from across the U.S.

- The sampling procedures are designed to provide samples that are representative. In general, market basket surveys conducted in this way with sample collection occurring at the point of retail purchase and analysis performed on a single-item basis are expected to assist in the characterization of pesticide residues in or on foods consumed by the U.S. population.

- EPA reviews these data and consults with the preparers of the reports in order to validate the data and prepare a written analysis. This type of review is conducted for all pesticide residue market basket data submitted to the Agency.

EPA also in some cases uses measured residue data from one commodity to represent residues on a similar commodity for which measured residue data are not available. For example, residue data for cauliflower might be used for broccoli if the pesticide use pattern is similar. This procedure is called "translation" of data.

Currently, OPP routinely uses DEEM™ software in its food risk assessments. The following review of DEEM™'s methodologies will assist with understanding how EPA conducts its food exposure assessments.

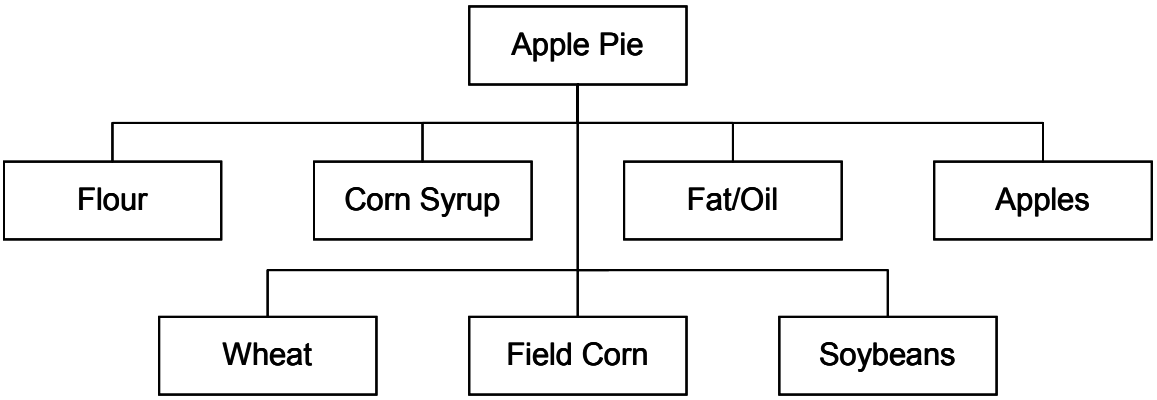
The two major inputs into the food exposure assessment are information on what food is eaten by representative individuals and in what quantity; and information on pesticide residues estimated to be on that food. The consumption information includes exactly what each individual ate as well as demographic information (e.g., age, sex, weight) on each individual. The residue files contain information on the residues expected on food. Estimates of resulting exposure (which represents the combining of data on food consumed with pesticide concentrations in those foods) are generated for the general U.S. population and specific sub-populations (e.g., children) using the demographic and other information available for each individual in the CSFII survey. In addition, self-reported body weight is used to convert exposure in milligrams (mg) of pesticide per day into mg of pesticide per kilogram (kg) of body weight per day, so that it can be compared to a toxicological endpoint expressed in mg pesticide per kg body weight per day.

Preliminary Steps

Consumption Data Adjustments

Respondents in the CSFII survey report what they ate in the form the food was eaten (e.g., apple pie). DEEM™ includes recipes and formulas that allow it to convert these foods to their components (e.g., apples, wheat, field corn, etc.), since residues are measured on these components. Using a very simplified example, the reported consumption of "apple pie" might become four components or food forms (apples, wheat, field corn, and soybeans) for which residue data are available. The actual recipes account for many more ingredients than illustrated here. The following diagram illustrates this process.

Figure 1



In addition to breaking down "as eaten" foods into their components, the recipes include the quantity of each ingredient. The following table shows the results of this conversion process for one hypothetical person's diet for one day.

"Agricultural Commodity Form" of Person #1's Day 1 Diet

Food or Food Form	Grams Consumed
Potatoes	40
Wheat	30
field corn	3
Soybean	1
Peaches	25
Carrots (cooked)	20

For each person in the CSFII who has completed two day records of food consumption, DEEM™ converts each day's food consumption as illustrated above, resulting in a large sample of data on what and how much people eat.

Residue Data Adjustments

The residues may be adjusted to more closely reflect the residues that may actually be consumed. These adjustments may include:

- accounting for residue changes resulting from cooking and processing;
- adjusting the distribution of measured residues (e.g., residues from field trial data) to ensure that they accurately reflect the percent of the crop treated; and
- deciding how to handle such issues as non-detectable residues and "blended" commodities such as juice.

The following two examples illustrate the concepts behind these adjustments. Note that other types of adjustments are possible.

- **Adjustments for cooking and processing**, to account for the fact that residues are not necessarily measured on the food in the same form that the food is consumed. Data may be available that show how various types of processes affect residues. For example, residues can be reduced as the result of washing, peeling, and cooking food. Residues may be concentrated by some processes, such as drying. Data are often available which result in "factors" that describe the change in residues from a particular processing method.

  For example Person #1 reports eating cooked carrots. The available residue data reflect raw carrots, but a processing factor is available showing the effect of cooking on carrot residues. Therefore, the residues for raw carrots will be adjusted using the cooking factor to create a new residue file for the food form cooked carrots. This cooking factor will reflect the reduction in the residues on raw carrots that results from cooking. DEEM™ will then adjust the raw carrot residue to account for this cooking factor when selecting a residue value for cooked carrots.

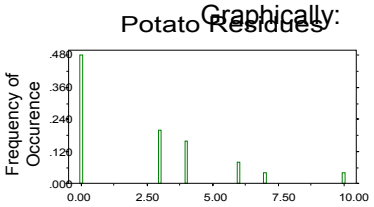
  For assessments that rely heavily on monitoring data, the adjustments for cooking and processing are the major adjustments that will be made to the residues. However, depending on the type of analysis being done and the residue data being used, other adjustments of the residues may be made. One specific example is adjusting for the percent of a crop that is treated. This adjustment takes into account the fact that not all of a crop is treated. Thus, a portion of the crop (the part that was not treated) will have no residue.

- **Adjustments for percent crop treated** involve including residue values equal to zero in the distribution of residues to reflect the percentage of the crop that is not treated. For example if 60% of the crop is treated, then 40% (100 - 60) is not treated. In this case, 40% of the residue values would be zeros, to reflect the fact that if the crop was not treated with the pesticide, it should not have any residues of that pesticide. This type of adjustment is generally used with field trial data, so that the right proportion of zeros are used in the analysis. This type of adjustment is slightly modified when monitoring data are used directly in the assessment, because monitoring data already reflect the percent of the crop that was treated.

After all of the residue files have been adjusted, as appropriate, and files have been developed for all of the foods and food forms necessary for the assessment, the result is a universe of residue files, one for each food or food form. The residue values may look like the following:

Potatoes

Graphically:



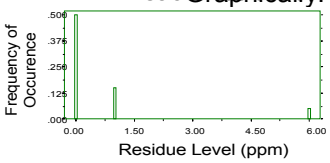
DEEM™ Sees as a List of Residue Values:

3 ppm	4 ppm	10 ppm
3 ppm	4 ppm	
3 ppm	4 ppm	
3 ppm	6 ppm	
3 ppm	6 ppm	
4 ppm	7 ppm	

and 12 residue values of 0 ppm

Peaches

Graphically:



DEEM™ Sees as a List of Residue Values

1 ppm	4 ppm
1 ppm	4 ppm
1 ppm	5 ppm
2 ppm	6 ppm
2 ppm	
2 ppm	

and 10 residue values of 0 ppm

etc., For All of the Foods and Food Forms in the CSFII

Illustrated below is an actual DEEM™ file, with the elements discussed above.

NOTE

Totalnz = the number of residue values that are NOT equal to zero–10 in this case. They are listed in the file below.

Totalz = the number of residue values that are zero– 10 in this case–meaning that in 50% of the Monte Carlo iterations zero is chosen as the residue value

```
Peaches
totalnz=10
totalz=10

1
1
1
2
2
2
4
4
5
6
```

```
Potatoes
total nz=13
total z=12

3
3
3
3
3
4
4
4
4
6
6
7
10
```

NOTE

Totalnz = the number of residue values that are NOT equal to zero–13 in this case. They are listed in the file below.

Totalz = the number of residue values that are zero – 12 in this case – meaning that in slightly less than 50% of the Monte Carlo iterations zero is chosen as the residue value

Fresh agricultural products and processed foods are widely distributed, and are assumed to be "national" commodities. Therefore, in the analysis the same residue files are used for every person.

Exposure Calculations

The following relationship is used to combine consumption and residue information to estimate exposure:

Exposure = Consumption X Residue

The calculations to estimate exposure are performed using a Monte Carlo approach–taking multiple repeated samples from the input files to generate an output distribution representative of any 1-day exposure for food, for the population of concern. The inputs for consumption are treated as fixed values. That is, as the iterative sampling is performed, reported consumption by an individual does not vary–it is what the individual reported consuming for that day of the survey. As a result, all diets in DEEM™ are "real." That is, the diets represent actual reported consumption for a specific person. There are no unrealistic combinations or combinations that would not normally occur (such as mashed bananas and caviar!!). The residue that may be on any item consumed that day is drawn from a distribution.[14] As shown in the following example, the residue values are randomly selected from all of the possible values in the residue distribution file for that food form.

Example Calculation

To make the following example simple enough to illustrate, we are using only two of the foods consumed by Person #1, and the very small residue files that were created for this example. Combining the consumption information with the residue information for the first Monte Carlo sampling iteration for Person #1, who reported eating potatoes and peaches, we might have:

[14]DEEM™ also permits users to use a single value for a residue. This is what is termed a "deterministic assessment" in OPP. Since that single value which is entered into the file is generally at a tolerance or some "realistic high end" level, this is a very conservative (health protective) value. It is not generally used for individual chemical risk assessments.

Food Consumed

Residues on Potatoes

Potatoes: 40 grams

{ a randomly selected residue value from the potato residue file

3 ppm	4 ppm	0 ppm	0 ppm
3 ppm	4 ppm	0 ppm	0 ppm
3 ppm	6 ppm	0 ppm	0 ppm
3 ppm	6 ppm	0 ppm	0 ppm
3 ppm	7 ppm	0 ppm	
4 ppm	10 ppm	0 ppm	
4 ppm	0 ppm	0 ppm	

In this iteration, DEEM™ randomly selects 0 ppm as the residue value from this residue file. Therefore, the exposure estimated from potatoes, on this iteration, is:

40 grams x 0 ppm = 0 mg

Residues on Peaches

Peaches: 25 grams

{ a randomly selected residue value from the peach residue file

1 ppm	4 ppm	0 ppm
1 ppm	5ppm	0 ppm
1 ppm	6 ppm	0 ppm
2 ppm	0 ppm	0 ppm
2 ppm	0 ppm	0 ppm
2 ppm	0 ppm	0 ppm
4 ppm	0 ppm	

In this iteration, DEEM™ randomly selects 2 ppm as the residue value from this residue file. Therefore, the exposure estimated from peaches, on this iteration, is:

25 grams x 2 ppm = 0.05 mg

To obtain person #1's total exposure estimate for this iteration (on a mg pesticide/kg body weight basis), for this day, based on this random sampling of residues:

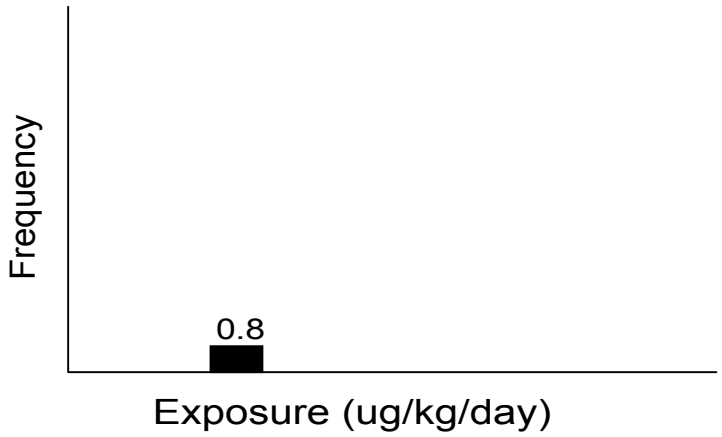
- Add together all of the exposures from all of the food forms consumed that day:

  0 mg + 0.05 mg = 0.05 mg

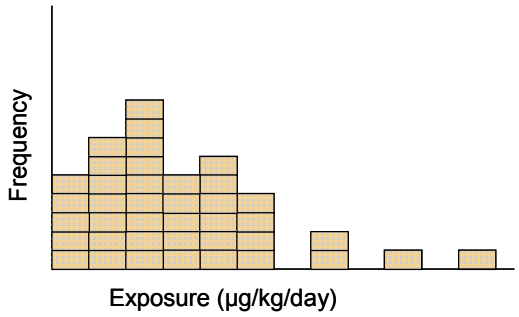
- Divide by Person #1's (self-reported) body weight (62 kg as reported in the CSFII, for example) to get exposure in mg/kg (of body weight)/day:

  0.05 mg/62 kg = 0.806 μg/kg/day = 0.000806 mg/kg/day

- Place this exposure number (0.806 μg/kg/day) on a graph as illustrated below.

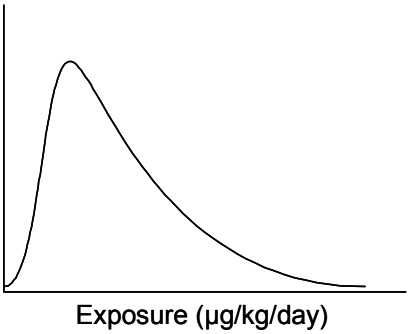


To begin to fill in the rest of the exposure distribution, these calculations are repeated approximately 1000 times for person #1's day one diet. Each time the calculation is repeated, the diet (that is the food forms and the amount of the food forms) of this individual remains the same while the residues are randomly selected from the residue distribution for each food form. Each of these "iterations" is a representation of "what might-have-been," that is, what pesticide residues that person might have been exposed to on that day. This process fills in the exposure distribution with approximately 1000 additional points. Taken together, these "might-have-beens" represent a collection of potential exposure events that portray the universe of exposures for this individual on this day. The process is then repeated another approximately 1000 times for Person #1 using the diet he reported on the second day of the survey, to generate another approximately 1000 points. These individual estimates continue to accumulate on the frequency histogram (i.e., the graph of the frequency distribution) and "build up" an exposure distribution, as illustrated below.



To complete the analysis, the process is then repeated approximately 1000 times for Person #2 using the diet that person reported on the first day of the survey and the same universe of residue files. Each of the estimated daily exposures is divided by the person's reported body weight and added to the distribution of estimated one day exposures. The process is repeated for day 2 of the survey for Person #2. The process is repeated for each person in the survey for both days of daily food consumption he or she reported, creating approximately 2000 potential exposure values per person.

When all of these exposure calculations are done, the graph will contain enough estimated values to approximate the total distribution of all one-day exposures for the population of concern. Sufficient iterations are conducted to ensure that the final estimates are "stable," that is, conducting additional iterations will have no effect on the resulting exposure distribution. Experience has shown that approximately 1000 iterations for each person-day are generally sufficient. The end result is a distribution of exposures for the U.S. population that represents the range and frequency of daily exposures that might be expected on any day, as illustrated below.

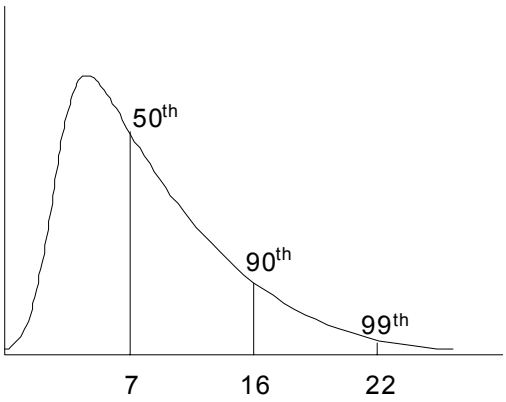


To obtain the relevant distributions for various sub-populations of concern, e.g., females 13 years and older, only the individuals who are members of that sub-population, e.g., females at least 13 years old, are considered.

Estimating Percentiles of Exposures/Calculating Percent RfD or acute PAD

Estimating Percentiles of Exposure

The above exposure distribution is used to obtain the exposure level(s) used in the risk assessments. To estimate percentiles, the distribution can be divided into 100 parts in such a way that each part represents 1% of the "person days" in the population (this is termed a percentile). Any desired percentile of exposure can then be determined from the distribution.



For example, reading off the above exposure distribution:

- The 50th percentile is that exposure level where 50% of the exposures are less, and 50% are greater than that level. In this case, 50% of the population of concern would be expected to be exposed to less than or equal to 7 μg/kg/day on any given day and 50% would be expected to be exposed to greater than 7 μg/kg/day.

- At the 90th percentile of exposure (in this case 16 μg/kg/day), 90% of the population would be expected to be exposed to less than or equal to 16 μg/kg/day, and 10% would be exposed to greater than 16 μg/kg/day on any given day.

- At the 99th percentile of exposure (in this case 22 mg/kg/day) 99% of the population is expected to be exposed at 22 μg/kg/day or less while 1% of the population is expected to be exposed at a level greater than 22 μg/kg/day on any given day.

In the risk assessment for one-day exposure the selected exposure percentile(s) as described above is compared to the toxicological endpoint (effect) of concern. This can be done in several ways including, for example, as Margins of Exposure (MOEs), as a percentage of the Reference Dose (%RfD), or as a percentage of the Population Adjusted Dose (%PAD). These latter two are illustrated below.

Calculating Percentages of the Acute Reference Dose (%aRfD) or Acute Population Adjusted Dose (%aPAD)

If the risk is expressed as a percentage of the acute Reference Dose (%aRfD) or acute Population Adjusted Dose (%aPAD), some or all of the uncertainty/safety factors are included in the estimated risk. In the case of the Reference Dose, all uncertainty factors, except the FQPA safety factor, are included. The Population Adjusted Dose includes all uncertainty factors as well as the FQPA safety factor.

If the %aRfD is used to express risk, first the aRfD is calculated as:

$$\text{aRfD} = \frac{\text{Endpoint (e.g., a NOAEL)}}{\text{Uncertainty Factors}}$$

If the uncertainty factor = 100, then in our example:

$$\text{aRfD} = \frac{7500\ \mu\text{g/kg/day}}{100} = 75\ \mu\text{g/kg/day}$$

To express the risk as a percentage of the aRfD, the following calculation is used:

$$\%\text{aRfD} = \frac{\text{Exposure (at selected percentile of exposure)}}{\text{aRfD}} \times 100$$

$$\%\text{aRfD} = \frac{22\ \mu\text{g/kg/day}}{75\ \mu\text{g/kg/day}} \times 100 = 29\%$$

Since the result is less than 100% of the acute reference dose, the risk estimate does not exceed the level of concern in this case.

The %RfD calculation does not contain any consideration of the FQPA safety factor. If the FQPA safety factor is incorporated into the risk estimate, then the aRfD is converted to an acute Population Adjusted Dose, using the following calculation:

$$\text{aPAD} = \frac{\text{aRfD}}{\text{FQPA Safety Factor}}$$

If the FQPA Safety Factor were retained at 10X then, in our example,

$$\text{aPAD} = \frac{75\ \mu\text{g/kg/day}}{10} = 7.5\ \mu\text{g/kg/day}$$

The percent of the aPAD is then calculated in the same way as the percent of the aRfD:

$$\%\text{aPAD} = \frac{\text{Exposure (at selected percentile of exposure)}}{\text{aPAD}} \times 100$$

In our example the result (at the 99.9^{th} percentile of exposure) would be,

$$\%\text{aPAD} = \frac{22\ \mu\text{g/kg/day}}{7.5\ \mu\text{g/kg/day}} \times 100 = 293\%$$

Since the result is greater than 100% of the acute reference dose, the risk estimate exceeds the level of concern in this case.

U.S. Environmental Protection Agency Ver. 7.74
DEEM ACUTE Analysis for CHEMICAL X (1994-98 data)
Residue file: prob.RS7 Adjustment factor #2 NOT used.
Analysis Date: 03-19-2002/16:14:17 Residue file dated: 03-19-2002/16:05:07/8
Daily totals for food and foodform consumption used.
MC iterations = 1000 MC list in residue file MC seed = 10281
Run Comment: "This is a run for use as an example."

Summary calculations (per capita):

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	% aRfD	Exposure	% aRfD	Exposure	% aRfD
U.S. Population:	0.002339	1.17	0.012146	6.07	0.035972	17.99
All infants:	0.005619	2.81	0.034172	17.09	0.074200	37.10
Children 1-6 yrs:	0.004990	2.50	0.024003	12.00	0.059066	29.53
Children 7-12 yrs:	0.001861	0.93	0.013394	6.70	0.038874	19.44
Females 13-50 yrs:	0.001443	0.72	0.010705	5.35	0.025547	12.77
Males 13-19 yrs:	0.000096	0.05	0.014564	7.28	0.061298	30.65
Males 20+ yrs:	0.002229	1.11	0.010142	5.07	0.025381	12.69
Seniors 55+:	0.003547	1.77	0.010385	5.19	0.021556	10.78

U.S. Environmental Protection Agency Ver. 7.74
DEEM ACUTE Analysis for CHEMICAL X (1994-98 data)
Residue file: prob.RS7 Adjustment factor #2 NOT used.
Analysis Date: 03-19-2002/16:14:17 Residue file dated: 03-19-2002/16:05:07/8
Acute Reference Dose (aRfD) = 0.200000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 1000 MC list in residue file MC seed = 10281
Run Comment: "This is a run for use as an example."

U.S. Population	Daily Exposure Analysis /a (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.000483	0.002809
Standard Deviation	0.002836	0.006343
Percent of aRfD	0.24	1.40

Percent of Person-Days that are User-Days = 17.20%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.000000	0.00	90.00	0.008614	4.31
20.00	0.000000	0.00	95.00	0.013285	6.64
30.00	0.000000	0.00	97.50	0.018790	9.39
40.00	0.000000	0.00	99.00	0.028512	14.26
50.00	0.000026	0.01	99.50	0.037954	18.98
60.00	0.000437	0.22	99.75	0.048541	24.27
70.00	0.002153	1.08	99.90	0.065848	32.92
80.00	0.004620	2.31			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.000000	0.00	90.00	0.000000	0.00
20.00	0.000000	0.00	95.00	0.002339	1.17
30.00	0.000000	0.00	97.50	0.006440	3.22
40.00	0.000000	0.00	99.00	0.012146	6.07
50.00	0.000000	0.00	99.50	0.017447	8.72
60.00	0.000000	0.00	99.75	0.024301	12.15
70.00	0.000000	0.00	99.90	0.035972	17.99
80.00	0.000000	0.00			

a/ Analysis based on all two-day participant records in CSFII 1994-98 survey.

U.S. Environmental Protection Agency Ver. 7.74
DEEM ACUTE Analysis for CHEMICAL X (1994-98 data)
Residue file: prob.RS7 Adjustment factor #2 NOT used.
Analysis Date: 03-19-2002/16:14:17 Residue file dated: 03-19-2002/16:05:07/8
Acute Reference Dose (aRfD) = 0.200000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
MC iterations = 1000 MC list in residue file MC seed = 10281
Run Comment: "This is a run for use as an example."

Children 1-6 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000939	0.004724
Standard Deviation	0.004960	0.010289
Percent of aRfD	0.47	2.36

Percent of Person-Days that are User-Days = 19.88%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.000000	0.00	90.00	0.015278	7.64
20.00	0.000000	0.00	95.00	0.024070	12.04
30.00	0.000000	0.00	97.50	0.033788	16.89
40.00	0.000000	0.00	99.00	0.048147	24.07
50.00	0.000066	0.03	99.50	0.059113	29.56
60.00	0.000746	0.37	99.75	0.071412	35.71
70.00	0.003030	1.52	99.90	0.089105	44.55
80.00	0.007438	3.72			

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Percent of aRfD

Percentile	Exposure	% aRfD	Percentile	Exposure	% aRfD
10.00	0.000000	0.00	90.00	0.000060	0.03
20.00	0.000000	0.00	95.00	0.004990	2.50
30.00	0.000000	0.00	97.50	0.012695	6.35
40.00	0.000000	0.00	99.00	0.024003	12.00
50.00	0.000000	0.00	99.50	0.033735	16.87
60.00	0.000000	0.00	99.75	0.044619	22.31
70.00	0.000000	0.00	99.90	0.059066	29.53
80.00	0.000000	0.00			

potatoes
totalnz=13
totalz=12

3
3
3
3
3
4
4
4
4
6
6
7
10

Peaches
totalnz=10
totalz=10

1
1
1
2
2
2
4
4
5
6

Appendix 4

Appendix 4: References and Suggested Readings

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