Guidance for Submission of Probabilistic Exposure Assessments to the Office of Pesticide Programs' Health Effects Division

Office of Pesticide Programs,
U.S. Environmental Protection Agency

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1. PURPOSE

U.S. EPA ("the Agency") recently established a policy and a series of guiding principles for the use of probabilistic risk assessment techniques. The Agency determined that probabilistic analysis techniques, "given adequate supporting data and credible assumptions, can be viable statistical tools for analyzing variability and uncertainty in risk assessments." (Memo, Fred Hansen, Deputy Administrator, May 15, 1997) The Agency also established a baseline set of conditions that must be met before the Agency will accept a probabilistic analysis for review and evaluation; these conditions relate to the good scientific practices of transparency, reproducibility, and the use of sound methods (Policy for Use of Probabilistic Analysis in Risk Assessment, U.S. EPA Office of Research and Development, May 15, 1997). This Agency Policy Document noted that Monte Carlo analysis is the probabilistic technique most frequently encountered, but other probabilistic techniques will not necessarily be excluded from consideration.

The purpose of this Guidance document is to establish standards for submissions of probabilistic human health exposure assessments to the Health Effects Division (HED) of the Agency's Office of Pesticide Programs (OPP). OPP management is committed to obtaining the capability for the Office to conduct its own Monte Carlo assessments. However, the Division currently allows submissions from chemical registrants using probabilistic techniques in one specific category (acute dietary risk assessment), and registrants have voluntarily submitted such analyses for other categories (risk assessment of occupational or residential exposures). This document is designed to provide interim guidance on general concepts for the preparation and review of probabilistic assessments. This document is not intended to provide step-by-step instructions on conducting probabilistic assessments; as HED gains greater experience in reviewing such assessments, more detailed guidance may be provided in the future. In addition, the Agency encourages the continued development of probabilistic risk assessment techniques. This Guidance is not intended to inhibit the advancement of the science, but rather to provide interim guidance as the science develops.

2. AGENCY POLICY FOR PROBABILISTIC ASSESSMENTS

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 (Agency Policy Document, 5/15/97). More complex analyses require greater resources, and probabilistic assessments can represent high levels of complexity. In a deterministic assessment, exposure is expressed as a single value, which could represent an upper-bound scenario (for example, tolerance levels on foods for dietary exposure), or a statistical tendency (for example, average values from appropriate field trial data). If a deterministic analysis based on conservative assumptions leads to risk estimates that are below levels of concern, then there is no need to refine risk assessments with more complex techniques.

In contrast to deterministic techniques, probabilistic risk assessments more fully consider ranges of values regarding potential exposure, and then weight possible values by their probability of occurrence. Individual input values used to generate a point estimate are replaced by a distribution reflecting a range of potential values; a computer simulation then repeatedly selects individual values from each distribution to generate a range and frequency of potential exposures. The output is a probability distribution of estimated exposures, from which exposures at any given percentile can be determined. Consideration of probabilistic analyses will be limited to exposure assessments. In accordance with Agency policy at the current time, such techniques will not be considered for dose-response evaluations of toxicological data.

The Agency Policy Document (5/15/97) designated eight conditions for acceptance of probabilistic analysis techniques. The Policy Document also identifies guiding principles specific to Monte Carlo analyses, and these should be considered in HED exposure assessments, as applicable. The eight general conditions are summarized below, amplified with some comments relevant to consideration of probabilistic assessments by HED:

1. The purpose and scope of the assessment should be clearly articulated in a "problem formulation" section that includes a full discussion of any highly exposed or highly susceptible subpopulations evaluated (e.g., children, the elderly). The questions the assessment attempts to answer are to be discussed and the assessment endpoints are to be well defined.

2. The methods used for the analysis, including models used, data upon which the assessment is based, and assumptions that have a significant impact upon the results, are to be documented and easily located in the report. This documentation should include a discussion of the degree to which the data are representative of the population under study. Also, documentation should include names of models and software used to generate the analysis. Routes of exposure should be clearly defined. Sufficient information is to be provided to allow the results of the analysis to be independently reproduced.

3. The assessment should include a sensitivity analysis, which is an evaluation of how the overall exposure distribution changes as individual inputs, expressed as distributions, are varied. The results of sensitivity analyses are to be presented and discussed in the report, in order to better determine which inputs drive the predicted risk. Probabilistic techniques should be applied to chemicals, pathways, and factors of importance to the assessment as determined by sensitivity analyses or other basic requirements for the assessment.

4. The presence or absence of moderate to strong correlations or dependencies between the input variables is to be discussed and accounted for in the analysis, along with the effects these have on the output distribution.

5. Information for each input and output distribution is to be provided in the report. This includes tabular and graphical representations of the distributions (e.g., probability density function and cumulative distribution function plots) that indicate the location of any point estimates of interest (e.g., mean, median, 95th percentile). The selection of distributions is to be explained and justified. For both the input and output distributions, variability and uncertainty are to be differentiated where possible.

6. The numerical stability of the central tendency and the higher end (tail) of the output distributions are to be presented and discussed.

7. Calculations of exposures and risks using deterministic (e.g., point estimate) methods are to be reported if possible. Providing these values will allow comparisons between the probabilistic analysis and past or screening level risk assessments. Further, deterministic estimates may be used to answer scenario specific questions and to facilitate risk communication. When comparisons are made, it is important to explain the similarities and differences in the underlying data, assumptions, and models.

   Point estimates, even if they represent a high-end exposure assessment, can provide important information to risk managers. If a particular exposure pathway is responsible for a significant risk, then mitigation could focus on that pathway.

8. Since fixed exposure assumptions (e.g., exposure duration, body weight) are sometimes embedded in toxicity metrics (e.g., Reference Doses, cancer potency factors), the exposure estimates from the probabilistic output distribution should be consistent with the toxicity metric.

3. GENERAL CONSIDERATIONS FOR PROBABILISTIC ASSESSMENTS

In addition to the conditions established by Agency Policy in the previous section, additional general guidance concerning data distributions, data sources, toxicity, and exposed populations is appropriate for probabilistic assessments submitted to HED. These considerations are more fully described below.

3.1 Data Distributions

In probabilistic analyses submitted to OPP to date, inputs in most cases have represented collections of discrete data, rather than continuous distributions. An example of such discrete data are residue values from a set of composite samples from field trials. Assessments submitted to date have typically used the data values themselves directly, assigning equal probability of selection, as justified, to each data point. Such discrete data distributions are entirely acceptable, and there is no requirement for registrants to fit a collection of samples to a mathematical model. Moreover, the Agency Policy Document (5/15/97) advises that there may be no single criterion for demonstrating "best fit" of a collection of data points to mathematical models for particular types of distributions.

However, if registrants desire to conduct probabilistic assessments where data inputs are mathematical models of distributions, they may do so provided appropriate criteria are met. Once input data are collected for an exposure variable of interest, a number of techniques are available for representing the variable as a continuous function. Two of these techniques are summarized below, and criteria for justifying the expression of distributions as specific mathematical models are described in more detail in Attachment 3 concerning distributions:

- An assessment may use the data to define a linear interpolated empirical distribution function (EDF). In this case, the data values themselves are used to specify a continuous cumulative distribution and the entire *range* of values (including intermediate points) is used as the input. With this technique, *any* value between the minimum and maximum observed values can be selected and model input is not limited to the specific values present in the measured data.

- An assessment may attempt to fit a mathematical expression to the data using standard statistical techniques, and input values can be selected from this fitted distribution.

The choice of input distribution should always be based on all relevant information (both qualitative and quantitative) available for an input. The selection of a distribution form should consider the quality and quantity of the information in the database, and should address broad

questions such as the mechanistic basis for choosing a distributional family, the discrete or continuous nature of the variable, and whether the variable is bounded or unbounded. In all cases, input values expressed as a distribution should be fully described.

We note, however, that not all input values need, or should, be expressed as a mathematically-modeled distribution and probabilistic techniques should be used only on those pathways and exposure patterns which may significantly influence the final risk. If an input variable does not significantly affect an exposure estimate regardless of its distribution, then its use in a probability distribution represents marginal value added. A sensitivity analysis should be performed to identify variables with significant effects on an assessment.

3.2 Data Sources

The sources for data used in an assessment should be clearly identified. Where these are studies that have previously been submitted to OPP, and/or reviewed by the Agency, identifying information such as petition number, reregistration submission, document number (MRID), or Agency review number should be provided, so the data points used may be readily confirmed.

Where available data points have been excluded from the probabilistic analysis, the exclusion should be identified and justified. In general, HED will not allow exclusion of data points as "outliers" based on statistical tests only; the decision to discard an outlier should be based on a scientific or quality assurance basis, and should only be done with extreme caution, particularly for environmental data sets which often contain legitimate extreme values. We believe that statistical tests can be used to identify suspect data points which require further investigation, but that it is inappropriate to eliminate outliers from analysis unless further review of the suspect points reveals a significant mistake in protocol which renders a field trial irrelevant to label conditions (e.g., wrong tank-mix concentration, mistaken application rate, too early a PHI, too many applications, etc.). This is particularly true in cases where the data points in question were used by the Agency in establishing a tolerance or other regulatory limit.

Registrants should also distinguish between data points based on independent individual samples, and replicate determinations or analyses of the same sample. Where replicates are reported, probability weighting of data from each individual sample should be equal (absent other justification), regardless of the number of replicate analyses for any one sample.

Studies from which data are obtained must contain sufficient quality assurance/quality control of data to assure sample integrity during treatment, collection, transportation, storage, and analysis. Examples of such assurance include validation of the analytical method used, or supporting storage stability data. Supporting data should be provided for summaries.

3.3 Toxicity

As noted above, current Agency policy does not allow probabilistic analysis of toxicity endpoints (Agency Policy Document, 5/15/97). Endpoints used in assessments should be consistent with the exposure of concern (acute, subchronic, chronic), and should be those selected by the HED Hazard Identification Assessment Review Committee, or selected in accordance with the Draft Toxicology Endpoint Selection Process: A Guidance Document, presented to the Science Advisory Panel in February 1997.

The population(s) of concern should be consistent with the appropriate toxicity endpoint. Where an effect is likely to be specific to a defined subpopulation, assessment should be targeted to that group. For example, since developmental effects are only likely to be expressed following exposure of a pregnant female, the appropriate subpopulation for assessment would be females, 13+ years old.

3.4 Exposed Populations

The complexity of probabilistic exposure assessments is demonstrated with the following two scenarios:

- Exposed individual, single chemical, single use, single route;
- Potential exposed individual, multiple chemicals, multiple uses, multiple routes.

As the complexity of the exposure assessment increases so does the potential of obscuring a highly exposed subpopulation; such subpopulations which are readily definable must be analyzed in a risk assessment. Consistent with the Agency Policy section above, probabilistic assessments should include bounding estimates for high exposure scenarios. Examples of highly exposed subpopulations include early reentry of individuals in treated areas, frequent users, and high volume users for occupational and residential assessments. For acute dietary assessments, examples include the small number of individuals who consume rare or less-popular agricultural commodities.

Risk managers should be advised of risk to highly exposed subpopulations, as well as to an overall population. Even if a small population is exposed to a high-end pathway, informing risk managers is appropriate because mitigation may become more achievable when risk applies to a small population.

4. ACUTE DIETARY ASSESSMENTS

At present, HED will consider for review submissions of probabilistic assessments on acute dietary exposure only; probabilistic analyses of chronic dietary exposure will not be reviewed. This policy stems from the limits of available data on chronic dietary patterns of the U.S. population. The surveys currently accepted by the Agency as sources for estimating food consumption by individuals (U.S. Department of Agriculture, National Food Consumption Survey (NFCS) 1977-78, Continuing Survey of Food Intakes by Individuals (CSFII) 1989-91, and when available, CSFII 1994-96) consist of data obtained over three or two days, respectively, based on questionnaires completed by consumers. OPP does not consider these data adequate to model chronic consumption patterns as distributions across the population. Frequently, foods are not consumed repeatedly by an individual sampled during the survey, and seasonality, personal preference and demographics make resampling of the data to generate surrogate chronic consumption of questionable validity.

Chronic dietary risk assessments are conducted by HED using a tiered approach, beginning with conservative assumptions and then proceeding through refinements to more closely reflect residue levels that might be eaten by the population of U.S. consumers. By the later iterations of the assessment, dietary risk is based on average consumption of foods (which may be categorized by population sub-groups), and a statistical evaluation of residues in specific foods (averages, or 95th percentile as specified). While available food consumption data will not capture the full range of chronic consumption, the statistical central tendencies should be sufficient to estimate chronic dietary risk. Even if probabilistic analyses were appropriate, they might provide additional information on the nature of a risk assessment distribution, but would not be expected to significantly alter conclusions based on central statistical tendencies. Probabilistic analyses therefore would not be expected to add significant value to chronic dietary risk assessments, and accordingly will not be reviewed at this time.

Acute dietary risk assessments are also conducted in a tiered approach (Final Office Policy for Performing Acute Dietary Exposure Assessment, Debra Edwards, HED, June 13, 1996). The HED Policy document defines input data for Tiers 1 and 2, representing deterministic assessments by the Agency, and for Tiers 3 and 4, where submission of probabilistic analyses by registrants is authorized. For these latter categories, the acceptable food consumption data (NFCS and CSFII) are considered suitable to represent population variation of consumption patterns on a daily basis.

Acceptable data sources, and/or data considerations, for acute dietary risk assessment are described below. The aforementioned policy document should be consulted for further details. :

4.1 Population of Concern

Acute dietary risk assessment as currently implemented by OPP focuses on population risk, not risk to the most highly exposed individual, and assumes that treated commodities are uniformly distributed in the food supply and a single exposure to treated commodities may be sufficient to cause an adverse effect in exposed individuals.

Acute dietary assessment focuses on population risk, and not risk to "eaters only". The use of the total population rather than "eaters only" allows consistent comparisons between different crop/residue combinations because the population of "consumers only" is different for every analysis. We recognize that the assessment of population-based exposure increases the potential for obscuring highly exposed consumers of certain infrequently-eaten commodities through "probabilistic dilution" among the entire population. When there is concern over commodities consumed by small numbers of people, the percent of the population consuming particular commodities should be reported; with this information, an estimate of the numbers of individuals at risk can be derived as readily from total population estimates as from consumers only estimates. In these cases the percentile level of regulatory concern can be raised to incorporate the high-risk eater population. This approach was endorsed by the OPP Science Advisory Panel in September 1995.

4.2 Reportable Percentile Exposure Values

OPP has made the determination that it is appropriate to regulate at the 99.9th percentile of exposure, when a probabilistic analysis is conducted for acute dietary exposure. This decision is consistent with Agency Guidelines for Exposure Assessment (57 FR 22888-22938, 5/29/92). While those Guidelines recommend caution in extrapolating beyond the 99th percentile of exposure, they indicate that for populations greater than 100, more stringent regulation may be warranted. Since the potentially exposed group may be the entire U.S. population, small portions of the exposed group can be large in magnitude. For example, 0.1% of U.S. children 1-6 consuming foods can represent dietary consumption by 23,000 children per day. Accordingly, regulation at the 99.9th percentile is warranted for probabilistic analyses.

Because of these considerations, it becomes more important for acute dietary assessments that probabilistic analyses demonstrate the stability of higher tail values (Number 6 under the Agency Policy section above). Changes in the 99.9th percentile value as the number of simulations increases should be clearly described. In keeping with Agency policy (5/15/97), information for such output and input distributions must include a tabular and/or graphic representation of various percentile exposures.

4.3 Food Consumption

The accepted sources NFCS 1977-78, CSFII 1989-1991, and when available, CSFII 1994-1996, are considered suitable to represent population variation of consumption patterns on a daily basis. CSFII 1987-88 is not considered a suitable data source because of an unacceptably low response rate.

4.4 Magnitude of the Residue

Residue data requirements specific to acute dietary assessment have also been established, and details are contained in the Office Policy document referenced above (Final Office Policy for Performing Acute Dietary Exposure Assessment, Debra Edwards, HED, June 13, 1996). To summarize the requirements for Tier 3 of acute dietary assessment, the first tier at which probabilistic analysis is used, residue values for non-blended single-serving commodities may be based on a distribution of field trial data points. For commodities that are typically mixed or "blended" prior to consumption, the average field trial value or the 95th percentile value from monitoring data may be used as a point estimate.

More detailed guidance on the acceptability of field trial data for exposure assessment is contained in the applicable policy document (Draft OPP Policy for the Use of Anticipated Residues of Pesticides in Foods for Use in Chronic Dietary Exposure Assessments, June 1997). Requirements for field trials are specified in OPPTS Test Guidelines, Residue Chemistry, 860.1500, August 1996.

4.4.1 Crop Field Trial Data

Office Policy has been previously issued (Ibid.) for Tier 3 analyses. Under this policy for non-blended (single-serving type) commodities, the distribution of residue data points from field trials should be based on individual field trials conducted at the least restrictive conditions allowed by the label (maximum rate for individual applications, maximum seasonal rate, shortest preharvest interval (PHI)). Preferred data sources are field trials that have been reviewed and accepted by the Agency (for example, for registration or reregistration actions). Registrants should clearly indicate sources of residue data (petition number, reregistration submission, MRID, Agency review number) so the data points used in acute assessment can be readily confirmed. Where data points from appropriate field trials have been excluded in the probabilistic analysis, such exclusion should be identified and justified.

The distribution of residue data points from field trials can be adjusted by percent crop treated values, reflecting the untreated part of a crop by introducing "zero" residues as a weighted proportion of the total number of residue entries. Imported crops are assumed to

be 100% treated unless data is provided. All percent crop treated values must be confirmed by OPP's Biological and Economic Analysis Division (BEAD).

4.4.2 Monitoring Data

In conducting its own exposure assessments with monitoring data, the Agency typically will use data from surveillance monitoring by the Food and Drug Administration (FDA), or data from the U.S. Department of Agriculture Pesticide Data Program (PDP). As noted previously for Tier 3 assessment of blended commodities, 95th percentile values from monitoring data may be used. PDP is designed to provide data relevant to dietary risk assessment, but it is limited to specific commodities and pesticides. Generally, at least 100 sample points for each commodity are required for monitoring data to be used in exposure assessment. Further details on monitoring programs are contained elsewhere (Draft OPP Policy for the Use of Anticipated Residues of Pesticides in Foods for Use in Chronic Dietary Exposure Assessments, June 1997).

For Tier 3, the Agency will not allow use of monitoring data as a distribution of residues for most raw commodities, because data from composite samples do not adequately represent the range of residues in a single serving size sample and the relationship between the residues measured in a composite sample and the range of residues in the individual samples that make up the composite is not established for most chemical/commodity combinations. From limited data that are available, OPP has observed that residues in single serving samples can be higher by an order of magnitude or more than residues in the corresponding composite sample. While field trial data are also based on composite samples, but they are generally measured at the "farm gate." Because residues may decline during shipping, handling, and/or processing before food consumption at the "dinner plate," field trial data are considered sufficiently conservative for use in an acute dietary risk assessment.

For Tier 4 analysis, assessment may include a distribution of monitoring data points, provided the residue data reflect a market basket survey based on single serving size samples. Such market basket surveys should be well-designed and statistically valid; study protocols should generally be approved by the Agency before initiation. As the Agency has already noted, a Tier 4 analysis may not necessarily result in lower acute risk estimates than Tier 3 (Final Office Policy for Performing Acute Dietary Exposure Assessment, Debra Edwards, HED, June 13, 1996).

4.5 Adjustments For "Typical" Use Patterns

As a further refinement, probabilistic assessments may include residue data based on "typical" application rates that may be more restrictive (lower rates, fewer applications, longer PHIs) than the maximum label conditions, provided certain conditions are met. Because the necessary conditions may require the generation of additional data, it may prove to the advantage of registrants and/or growers to conduct an informal sensitivity analysis to determine to what extent lower residue levels in given crops may influence overall acute dietary exposure. As one condition, OPP's BEAD must verify that the typical usage data are reasonable and reflect actual practice. For example, if a registrant assessment has been conducted under assumptions that 40% of the crop is not treated, that 40% is treated at a "typical" rate of 0.5x the label maximum, and 20% treated at the label maximum, all these assumptions should be confirmed by BEAD. For regions of production for which use/usage data are not available, or not confirmed by BEAD, residue levels should continue to be based on maximum label conditions for incorporation in the assessment.

As a second condition, residue data or residue decline data, as applicable, must be available to support the inclusion of "typical" use patterns. Assumptions of a linear or other relationship between application rates and resulting residue levels may not be made automatically; data correlating measured residue values to application rates must be provided. Likewise, an automatic assumption that residue decline is directly proportional to time is not acceptable; data must be provided to demonstrate a relationship between pre-harvest interval (PHI) and residue level. Data establishing residue decline curves cannot be derived from field trials conducted at different sites or at different times because of the potential impact of environmental conditions and variability in study conduct on results. Therefore, only data from controlled field trials specifically designed and collected to monitor the effects of PHI on residues can be used for modeling. Data provided should include weather and precipitation records to enhance evaluation of a study and its results.

Residue data to support the use of typical use/usage data may be derived from a number of sources. Ideally, at least two side-by-side field trials, comparing residues from the maximum label conditions v. applicable reduced conditions, should be conducted at locations previously used to support the label rate. The sites chosen should reflect different geographical regions, with one being the region where the highest average field trial (HAFT) value occurred for a given crop, and the second being the region representing the highest proportion of production for the given crop (see Tables in OPPTS Test Guidelines, Residue Chemistry, 860.1500, August 1996). If both these conditions occur in the same region, then the second field trial should be conducted in the region representing the second highest proportion of crop grown. Likely sources of field trial data include registrants own data and data from USDA's IR-4 program. Extrapolation of data between similar crops may be allowed on a case by case basis, considering similar cultural practices and application patterns.

Barring the availability of side-by-side field trials, data produced by commercial growers may also be useful in establishing the relationship between application rate and resulting residues. Such data may be used in probabilistic assessments, provided that they are collected using procedures documented in standard operating procedures, that samples can be clearly correlated with given application rates and/or conditions, that the PHI, time from harvest to analysis, commodity analyzed, and demonstrated storage stability of residues v. storage conditions used are clearly defined, and that the analytical method used is well defined (including its limit of quantitation (LOQ)), and detects all residues of current toxicological concern for a given pesticide. For acute dietary analysis, in no case may residue levels be extrapolated below the method LOQ.

As noted above, use of field trial data based on composite samples has been considered acceptably conservative for acute dietary assessment. Use of residue data from field trials under application conditions less stringent than the allowed label rate has the effect of diminishing this conservatism. Ideally, field trial data under reduced application patterns should be based on single serving size samples. Recognizing that such data are rarely available, HED will evaluate chemical-specific considerations to determine whether the use of data from composite samples is acceptable. The most important considerations would be the systemic nature of the pesticide, application type and timing (e.g., short PHI or postharvest fruit dip), and the stability of the pesticide (especially postharvest and during processing or cooking, as applicable), as these factors influence the likelihood that data on composited samples at harvest may underestimate residues in single serving size samples at the time of consumption. If examination of these and other factors lead the Agency to determine that use of composite samples may underestimate risk to one or more population subgroups, then other options would be pursued. These other options could include, but not be limited to: offering a registrant the opportunity to conduct a market basket survey under Tier 4; reverting to an exposure assessment based only on label maxima conditions; or calculation of worst-case residues in a single serving size component by assuming all residues of the composite sample can be attributed to a component single serving size sample.

It seems appropriate to advise registrants that data requirements under this section could be reduced if registrants change a label directly to incorporate more stringent conditions, and then conduct a probabilistic assessment using residue data based on the new label conditions only. In that case, the revised label would represent the new maximum conditions, and the assessment would represent a simple Tier 3 approach. Data (which could include limited bridging data) would still be required to justify residue levels under the new maximum conditions, but verification by BEAD, and data comparing residues in composite versus single serving size samples would not be required.

4.6 Exposure Assessment for Livestock Commodities

In assessments submitted to OPP, the following approach for estimating residues in livestock commodities has been accepted for Tier 3 analysis. This approach is not meant to be prescriptive; HED would consider other approaches to modeling livestock diets, provided they can be justified scientifically and remain protective of public health from the perspective of acute dietary risk:

The dietary burden for the appropriate animals should first be calculated in a manner similar to that for determining tolerances in meat, milk, poultry, and eggs (MMPE). That is, all feed items (as specified in OPPTS Test Guidelines, Residue Chemistry, 860.1000, August 1996, Table 1) that could be treated with the pesticide of interest should be assumed to have residues with 100% crop treated.

A reasonable worst case dietary burden should then be calculated taking into account the residue levels for individual feeds and their percentages of the diet with dry matter correction where appropriate. With respect to residue levels, for dairy cattle feed items the average residue from field trials reflecting the maximum use pattern may be used for all commodities to account for the extensive blending of milk. For beef cattle the average field trial residue may be used for blended feeds (e.g., grains), but the highest average field trial (HAFT) should be employed for non-blended feeds such as forage and hay. "Reasonable worst case" means that the diet should take into account regional practices (e.g., local milksheds), but should not be a mixture of feeds on which the animal would have difficulty surviving. For example, it should not consist primarily of similar feeds that are high in protein (e.g., combination of meals from soybeans, peanuts and cottonseed), or that are low in nutritional value (e.g., cotton gin byproducts plus rice straw plus sorghum stover).

If reliable percent crop treated (%CT) data are available for the feed items, this information may be used in the following manner. The worst case dietary burden described above may be assumed to apply to only that % of meat, milk, poultry and egg (MMPE) samples corresponding to the highest %CT for any one feed item. (This highest %CT should account for <u>all</u> feed items for the pesticide, not just those used to construct the worst case diet.) All other samples of animal products will be assumed to have zero residues. For example, if the %CT for alfalfa, soybeans and corn are 20%, 10%, and 5%, respectively, 20% of livestock commodities may be assumed to have residues and the remaining 80% assumed to have no residues. On a probabilistic basis, a much smaller percentage would receive the maximum dietary burden.

With respect to calculating the residue levels in animal tissues and eggs, the maximum ratio of tissue or egg residues to dose level from the feeding study should be used since these items may be consumed as a single commodity. That maximum ratio should normally reflect the samples from the feeding level closest to the worst case dietary burden provided there are quantifiable residues to calculate a ratio. A linear regression may also be used to determine residue levels provided the regression is forced through zero (i.e., shows no residues in animal commodities when dietary burden is zero). In the case of milk, it is acceptable to use the <u>average</u> ratio of

residues to dose level due to the high degree of blending that occurs for this commodity. That average ratio should be calculated using only those samples collected after residues have reached a plateau in the milk.

5. OCCUPATIONAL AND RESIDENTIAL EXPOSURE ASSESSMENTS

Prior to issuance of this guidance document, HED assessed occupational and residential exposure to pesticides using a deterministic approach, and as such would not consider for review submissions of probabilistic assessments on occupational and residential exposure. This policy stemmed from a lack of adequate criteria to assess the validity of probabilistic exposure assessments and a concern that highly exposed subpopulations might be obscured in population based assessments.

Consistent with current Agency policy that probabilistic analysis techniques are viable statistical tools for analyzing variability and uncertainty in risk assessments, HED has now developed guidance for the preparation and review of probabilistic exposure assessments from occupational and residential use of pesticides. Accordingly, HED will now accept for review probabilistic exposure assessments in support of occupational and residential use of pesticides.

However, registrants and reviewers should be aware that some regulatory restrictions are based on acute effects or incidence of pesticide poisoning. These restrictions may include certain articles of personal protective equipment (PPE) (e.g., protective eyewear), or minimum restricted-entry intervals which are based on the acute toxicity of the active ingredient. The Agency is unlikely to reduce or eliminate these types of protections regardless of the results of probabilistic analyses based upon other than acute toxicological endpoints.

For example, protective gloves may be required on product labeling because of a high incidence of skin irritation effects to workers handling the product. If a probabilistic risk assessment for this chemical concluded that workers are sufficiently protected from other effects at baseline attire (i.e., no gloves), the Agency would not be inclined to eliminate a glove requirement based on reported skin incidents. Or, a probabilistic risk assessment based on a short- or intermediate-term toxicological endpoint may indicate that by 12 hours following application, short- or intermediate-term risks to workers would not exceed the Agency's level of concern. If the product, however, has a longer REI based either on its acute toxicity (including its potential to cause skin or eye irritation) or poisoning incidents, the Agency would not be inclined to reduce the REI to 12 hours, despite the results of the probabilistic assessment.

5.1 Mixer/loader/applicator (M/L/A) exposure

Occupational exposures to pesticides from agricultural handling (mixer/loader/applicator) are assessed in a tiered manner consistent with HED policy described in *Series 875 - Occupational and Residential Exposure Test Guidelines, Group A-Applicator Exposure Monitoring Test Guidelines (Previously designated Subdivision U).* The Applicator Exposure Monitoring Test Guidelines describe studies and data required to determine dermal and inhalation exposure following agricultural use of a pesticide. These studies/data are: Dermal Exposure - Outdoors, Guideline 875.1100; Dermal Exposure - Indoors, Guideline 875.1200; Inhalation Exposure-Outdoors, Guideline 875.1300; Inhalation Exposure-Indoors, Guideline 875.1400; Biological Monitoring, Guideline 875.1500; Applicator Exposure Monitoring Data Reporting, Guideline 875.1600; and Detailed Product Use Information, Guideline 875.1700.

The Pesticide Assessment Guidelines, Subdivision U - Applicator Exposure Monitoring, states in part, "...respiratory exposure monitoring is required if the material in question has been demonstrated to cause an adverse biological effect that is associated with or accentuated by respiratory exposure; if the formulation or application method is expected to result in significant respiratory exposure; or if the formulation or application method has an unknown potential for respiratory exposure." Since respiratory exposure to pesticide handlers is generally much less significant in comparison to dermal exposure, this document will describe dermal input parameters only. It should be noted that input parameters for probabilistic inhalation exposure assessments could be derived in a similar manner.

Dermal exposure for an agricultural pesticide handler is initially determined as a baseline dermal unit exposure (long pants, long sleeve shirt, no gloves, open mixing/loading, and open cab tractor), followed, if necessary, by an assessment which takes into account additional personal protective equipment (PPE; double layer of clothing and chemical resistant gloves) and finally an assessment which takes into account engineering controls (closed mixing, single layer of clothing, no gloves, enclosed cockpit, enclosed cab, or closed mixing).

Input parameters for these assessments historically have been point estimates reflecting typical, maximum, or minimum values. Parameters generally entered into deterministic calculations for dermal exposure from handling pesticides in an agricultural setting are: the subpopulation of interest (e.g., mixers/loaders, re-entry workers, applicators, etc.); the unit exposure value for the subpopulation of interest (derived from PHED V1.1); the application rate (from product labels); lbs active ingredient handled and the area treated in a typical workday (estimates based on available usage information) and the worker's body weight (taken from the Agency's draft Exposure Factors Handbook).

It should be noted that frequency of exposure is not explicitly considered as an input parameter for short- or intermediate- term exposures because this assumption is implicitly accounted for in the duration of the toxicology endpoint. Additional details regarding these parameters both as

currently used in deterministic assessments and as might be used in a probabilistic assessment are described below:

- *Populations of Interest:* **Under the deterministic approach,** HED considers the MOEs for each individual subpopulation of exposed users (e.g., mixer/loaders, reentry workers, pilots). **Under a probabilistic approach,** the policy of assessing the risk to each individual subpopulation of interest will continue. Several exposure assessments can be required for a given subpopulation depending upon the number of toxicological endpoints that have been identified (e.g., cancer, short-term, intermediate-term, and chronic). The completion of assessments for short- and intermediate-term endpoints generally do not require an extensive knowledge of the population dynamic. For example, HED would not consider market-share data reflecting national use of a pesticide (e.g., percent crop treated) if a short- or intermediate-term endpoint exists, because any single exposure event may pose an unacceptable risk. The completion of chronic and cancer-based assessments does, however, require a more extensive knowledge of the population dynamic (i.e., market share) as these exposures must be amortized over a lifetime and market share information provides a valuable insight into the subpopulation over a lifetime. For example, market share information may provide a basis for assessing risks to migrant worker populations over a lifetime by delineating the use of chemicals on specific crops.

- *PHED values:* **Under the deterministic approach**, unit exposure values are derived from chemical-specific studies, and surrogate studies in PHED. If chemical- specific data are available, these data should be used in conjunction with PHED data, reflecting similar exposure scenarios, to derive unit exposure estimates (see PHED: The Pesticide Handler Exposure Database, Reference Manual, Version 1.1, February 1995, and The Pesticide Handler Exposure Database (PHED), Evaluation Guidance, Version 1.1, March 1995). PHED composite point estimates (unit exposure) are assumptions of central tendency values for each body part from replicate data. It should be noted that there is typically high variability among replicates in exposure studies and that most of the studies in PHED do not have exposure data for all body parts. Unit exposure values are derived from actual exposure studies where the same formulation types, equipment, and methods were employed. About half of workers doing the same activity would be expected to have *higher* unit exposures, and half would be expected to have *lower* unit exposures. **Under a probabilistic approach**, EPA will permit handler exposures to be estimated probabilistically. That is, the entire range of exposure values from PHED and chemical-specific studies can be considered and incorporated into the exposure assessment. However, exposure values derived from PHED V1.1 and chemical - specific studies must be fully

described with respect to the source and quality of the data, the subsetting of the data base, and the process by which data on individual body parts are aggregated to estimate total dermal exposure. Potential correlations between "body parts" and exposure values must be considered.

- *Application rates*: **Under the deterministic approach**, application rates are selected from available data. HED recognizes that varying rates can be applied depending upon a number of factors (including the degree of the pest problem and environmental considerations). Typical application rates, when available, are used to estimate intermediate and long term exposure. Maximum application rates are used to estimate acute and short term exposure. **Under a probabilistic approach,** EPA will permit application rates to be expressed as distributions, provided appropriate data are available and the distribution is fully described and statistically supported. Multiple values may be used in lieu of a fixed value when the data have been shown to be appropriate for the scenario being assessed. OPP's Biological and Economic Analysis Division (BEAD) must verify that application rates less than the maximum label rate reflect actual practice.

- *Treated area:* **Under the deterministic approach**, treated area per day for the various application method/crop combinations are standard values used by the former Occupational and Residential Exposure Branch. These values were developed after much internal discussion, and are considered to represent typical to reasonable high-end acreage. **Under a probabilistic approach**, this information can be broken down into its individual components. That is, acres treated per day is the product of workday length (in hours/day) and treatment rate (in acres/hour). This latter factor can be considered a function of tractor (or aircraft) speed, tank capacity, length of run, swath width, finished spray treatment rate, tank refill time, and distance to tank refill station. Workday length and treatment rate can be expressed as distributions, provided appropriate data are available and the distribution is fully described and statistically supported. Multiple values may be used in lieu of a fixed value when the data have been shown to be appropriate for the scenario being assessed. Potential correlations need to be considered. OPP, BEAD must verify that multiple values for treatment rate and acres treated reflect actual practice.

- Body weight: **Under the deterministic approach**, 70 kg value for adults or 60 kg for females is routinely used by the Agency. This is identified in the Agency's draft Exposure Factors Handbook as the mean body weight for both sexes of adults in all age groups combined, rounded to one significant figure. **Under a probabilistic approach,** EPA will permit body weights to be expressed

as distributions, provided the distribution is fully described and statistically supported.

5.2 Residential exposure

Residential exposure assessments generally reflect baseline exposure and do not consider additional personal protective equipment or engineering controls (i.e., short pants, short-sleeved shirts, no protective gloves, and no respiratory protection are baseline). Input parameters may reflect typical, maximum, or minimum values. Exposure to pesticides from residential uses are assessed in a **deterministic manner** consistent with HED policy described in: *Standard Operating Procedures for Residential Exposure Assessments* (presented to the SAP 9/97, and to be presented 3/98). This document describes algorithms for calculating potential dose rate (PDR) for typical residential exposure scenarios and summarizes (Appendix A) assumptions, input descriptors, references, and output descriptors for each scenario. PHED data are used to estimate unit exposure for only a limited number of the residential scenarios described.

Under a probabilistic approach, EPA will permit probabilistic assessment of exposed subpopulations. All input parameters for residential exposure assessments can be expressed as distributions, provided appropriate data are available and each distribution is fully described and statistically supported. Multiple values may be used in lieu of a fixed value when the data have been shown to be appropriate for the scenario being assessed. When PHED is used to determine baseline unit exposure, the entire range of unit exposures derived from a PHED analysis can be considered and incorporated into the exposure assessment. Unit exposure values (derived from PHED V1.1) must be fully described with respect to aggregating body part exposures, subsetting the data base, and quality of data (PHED: The Pesticide Handler Exposure Database, Reference Manual, Version 1.1, February 1995). Potential correlations between "body parts" and exposure values should be considered. Several exposure assessments may be required for a given subpopulation depending upon the number of toxicological endpoints that have been identified (e.g., cancer, short-term, intermediate-term, and chronic). The completion of assessments for short- and intermediate-term endpoints generally do not require an extensive knowledge of the population dynamic. For example, HED would not consider market-share data reflecting national use of a pesticide (e.g., percent households using the product) if a short- or intermediate-term endpoint exists, because any single exposure event may pose an unacceptable risk. The completion of chronic and cancer-based assessments does, however, require a more extensive knowledge of the population dynamic (i.e., market share and demographic data) as these exposures must be amortized over a lifetime and these data provide a valuable insight into the subpopulation over a lifetime. For example, market share information may provide a basis for assessing risks to residential populations over a lifetime by delineating the use of chemicals in specific geographical regions and across demographic groups. OPP, BEAD must verify market share data used to amortize long term exposure from residential use of pesticides.

5.3 Postapplication exposure

Post application exposure to pesticides from agricultural use generally reflects baseline exposure which for this scenario assumes clothing of long pants and long-sleeved shirts. Postapplication exposure to pesticides from residential use generally reflects baseline exposure which for this scenario assumes clothing of short pants and short-sleeved shirts. Additional PPE (gloves and respirators) and engineering controls are generally not considered effective options by HED except under very specialized circumstances. Input parameters may reflect typical, maximum, or minimum values. Exposure to pesticides from entering treated areas are assessed in a **deterministic manner** consistent with HED policy described in: *Series 875 - Occupational and Residential Exposure Test Guidelines, Group B*-Postapplication Exposure Monitoring Test Guidelines (previously designated Subpart K); and *Standard Operating Procedures for Residential Exposure Assessments*. The Postapplication Exposure Monitoring Test Guidelines describe studies and data required to determine reentry intervals following use of a pesticide. These studies/data are: Dislodgeable Foliar Residue (DFR) Dissipation Study, Guideline 875.2100; Soil Residue Dissipation (SRD) Study, Guideline 875.2200; Indoor Surface Residue (ISR) Dissipation Study, Guideline 875.2300; Dermal Exposure, Guideline 875.2400; Inhalation Exposure, Guideline 875.2500; Biological Monitoring, Guideline 875.2600; Product Use Information, Guideline 875.2700; Description of Human Activity, Guideline 875.2800. The Standard Operating Procedures for Residential Exposure Assessments describes algorithms for calculating potential dose rate (PDR) for typical residential postapplication exposure scenarios and summarizes (Appendix A) assumptions, input descriptors, references, and output descriptors for each scenario.

Under a probabilistic approach, EPA will permit probabilistic assessment of exposure to individuals entering pesticide treated areas (i.e., both occupational and residential scenarios). All input parameters for assessing exposure from entering treated areas can be expressed as distributions, provided appropriate data are available and each distribution is fully described and statistically supported. Multiple values may be used in lieu of a fixed value when the data have been shown to be appropriate for the scenario being assessed. Several exposure assessments may be required for a given subpopulation depending upon the number of toxicological endpoints that have been identified (e.g., cancer, short-term, intermediate-term, and chronic). The completion of assessments for short- and intermediate-term endpoints generally do not require an extensive knowledge of the population dynamic. For example, HED would not consider market-share data reflecting national use of a pesticide (e.g., percent crop treated or households using the product) if a short- or intermediate-term endpoint exists, because any single exposure event may pose an unacceptable risk. The completion of chronic and cancer-based assessments does, however, require a more extensive knowledge of the population dynamic (i.e., market share and demographic data) as these exposures must be amortized over a lifetime and these data provide a valuable insight into the subpopulation over a lifetime. For example, market share information

may provide a basis for assessing risks to occupational populations over a lifetime by delineating the use of chemicals in specific geographical regions across crops as the same population could provide hand labor services for various crops within a region. OPP, BEAD must verify market share data used to amortize long term exposure from entering pesticide treated areas.

Attachment 1: Glossary

Attachment 2 : Probabilistic Risk Assessment and Monte-Carlo Methods: A Brief Introduction

Attachment 3: Distribution Selection