CONSIDERATION OF THE FQPA SAFETY FACTOR AND OTHER UNCERTAINTY FACTORS IN CUMULATIVE RISK ASSESSMENT OF CHEMICALS SHARING A COMMON MECHANISM OF TOXICITY

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I. Introduction

A. Purpose of Document

This guidance document provides the Office of Pesticide Programs (OPP) current thinking on application of the provision in FFDCA section 408(b)(2)(C) regarding an additional safety factor for the protection of infants and children in the context of cumulative risk assessments. In an earlier science policy paper for individual chemicals, OPP addressed how its risk assessments will consider the FQPA safety factor provision for individual chemicals (USEPA 1999 and USEPA 2002a). Additionally, OPP has prepared guidance on how to conduct a cumulative risk assessment for two or more pesticides sharing a common mechanism of toxicity (USEPA 2002b). As discussed below, each of these papers provided some general information and guidance on the FQPA safety factor, but did not address in detail the application of the FQPA safety factor provision on cumulative risk assessment.

This document is intended to serve as a guide for OPP risk assessors to facilitate consistent implementation of the children's FQPA safety factor provision in cumulative risk assessments and to increase the regulated entities' and the public's understanding of OPP cumulative risk assessments. Importantly, this guidance document is a policy statement and not a legislative rule and thus is not binding on OPP or on outside parties. It does not predetermine any pesticide-specific decision regarding the FQPA safety factor in a cumulative risk assessment. OPP remains free to take actions that vary from the guidance provided in the document. For example, OPP may deviate from the document based on developments in science or risk assessment methodologies or changes in science policy approach. Any such action would be accompanied by an explanation for OPP's decision. Similarly, the regulated community and the public retain the right to object both to the manner in which the guidance document is applied to specific groups of pesticides as well as to the policy considerations underlying the guidance document. Such objections could address any factual, scientific, policy, or legal conclusions or interpretations in the guidance document. If such objections are persuasive, OPP will be guided by them in the specific decision at hand and also modify the policy, as appropriate.

OPP staff are cautioned that because this document is a guidance policy and not a binding rule, they must consider the merit of all contentions from outside parties regarding application of the FQPA safety factor to specific cumulative risk assessments. Should staff believe, for whatever reason, that action at variance from this guidance document should be taken, that recommendation should be flagged so that it can receive the full consideration of OPP decision-makers.

B. Legal Framework

The portion of FFDCA section 408 addressing exposure of infants and children to pesticide chemical residues, section 408(b)(2)(C), directs that EPA, in taking action regarding a tolerance, "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue ." Section 408(b)(2)(C)(ii)(I). This paragraph also explicitly requires EPA to assess the risk to children taking into account "available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity." Section 408(b)(2)(C)(i)(III). Finally, this paragraph mandates that, in making the reasonable certainty of no harm finding, EPA apply an additional tenfold margin of safety to take into account potential pre- and postnatal toxicity and completeness of the toxicity and exposure databases. A different factor may be applied if the safety finding is supported by reliable data. This is referred to as the "FQPA safety factor" provision.

A risk assessment addressing cumulative effects of residues of multiple pesticide chemicals that exhibit a common mechanism of toxicity will have a major bearing on OPP's determination of whether the "reasonable certainty of no harm" finding can be made. Accordingly, OPP will need to consider several of the core aspects of the cumulative assessment-the identification of the nature of the common toxic effect and the scope of the toxicity and exposure databases relative to the cumulative assessment -in determining whether reliable data exist justifying adjustment of the additional safety factor called for in this provision.

C. Terminology

This guidance document uses the terminology adopted in the guidance document titled *Determination of the Appropriate FQPA Safety Factor(s) For Use in the Tolerance-Setting Process* (USEPA 2002a). The terminology used distinguishes those safety factors introduced as a result of FQPA from traditional uncertainty factor practice in the Agency. It is important to recognize, however, that the FQPA safety factor, as defined in FQPA, does not stand wholly apart from traditional agency practice but rather incorporates that practice as a part of the safety factor. Thus, there is a large degree of overlap between the FQPA safety factor and traditional Agency practice as to the use of uncertainty factors to account for incomplete characterization of a chemical's toxicity.

A breakdown between the traditional and unique aspects of the FQPA factor is relatively straightforward when OPP has made an individualized determination of a "different" FQPA safety factor. Terminology to aid in distinguishing these traditional and unique aspects in a "different" FQPA safety factor is set forth below. In those instances, however, where the additional 10X FQPA safety factor is retained because the presumption in favor of applying an additional 10X is not overcome, differentiating the traditional and unique aspects of the FQPA safety factor may be quite difficult.

To capture both the standard and traditional aspects as well as the uniqueness of the FQPA safety factor, EPA has chosen to use the following terminology to describe the two components of the FQPA safety factor:

- **Standard uncertainty factors** are the 10X factors used to account for interhuman variation (intraspecies differences-UF_H) and experimental animal to human (interspecies-UF_A) differences. These uncertainty factors are not considered to be FQPA safety factors.

- **Traditional uncertainty factors** are those used prior to FQPA passage to account for database deficiencies (i.e., application of an uncertainty factor to extrapolate from subchronic to chronic data (UF_S) if deriving a chronic RfD); application of an uncertainty factor to extrapolate from the NOAEL to LOAEL (UF_L) if no appropriate NOAEL can be identified in the toxicology database; and application of a database uncertainty factor (UF_{Db})which is intended to account for the absence of key toxicological data) and which are now codified by FQPA; and

- **Special FQPA safety factor**s are used to apply to the aspect of a different FQPA factor (i.e., residual concerns for susceptibility and residual concerns in the exposure assessment) that is unique to FQPA, and which are those factors introduced primarily as a result of FQPA.

Any given FQPA safety factor may consist of traditional uncertainty factors used to address data deficiencies and the unique aspects of the special safety factor. By adopting this terminology EPA hopes that its safety factor determinations will be transparent. (Other important terminology to remember includes: (1) "presumptive" or "default" FQPA factor which refers to the default FQPA additional 10X safety factor that is mandated by the statute if OPP decides that there are not reliable data to choose a different factor; and (2) "additional" FQPA factor which is used to mean that all FQPA factors (including traditional uncertainty and special FQPA factors) are in addition to the inter- and intraspecies uncertainty factors.)

B. Background

OPP's revised policy document on *Determination of the Appropriate FQPA Safety Factor(s) For Use in the Tolerance-Setting Process* provides guidance on how OPP would implement the FQPA safety factor provision for individual chemicals (see USEPA 2002a). The document contains legal interpretations of key aspects of the FQPA safety factor provision and establishes a framework for making decisions about the need for the uncertainty factors used traditionally by the Agency in deriving RfDs and the FQPA safety factor. The FQPA safety factor guidance specifically restricted its applicability only to the consideration of the FQPA safety factor in the context of individual chemical risk assessments. It went on to state:

> *In the future, as approaches for conducting cumulative risk assessments are developed and applied, this document may require modification and updating to articulate the policies attendant to the FQPA safety factor in the assessment and regulation of chemicals sharing a common mechanism of toxicity.*

OPP discussed the relationship of the FQPA safety factor provision to the cumulative risk assessment process in more detail in its draft Cumulative Risk Assessment Guidance, made available to the public on June 30, 2000 (see USEPA 2000). In Sections 5.2 and 6.4.2 of the document, OPP discussed both the standard uncertainty factors applied in EPA risk assessments to account for interhuman variation (intraspecies differences) and experimental animal to human (interspecies) differences; and the FQPA safety factor that is intended to account for potential pre- and postnatal toxicity and the completeness of the toxicity and exposure databases. Encompassed with the FQPA safety factor are traditional uncertainty factors used to account for use of a Lowest-Observed-Adverse-Effect-Level (LOAEL) to estimate a No-Observed-Adverse-Effect-Level (NOAEL), use of a subchronic NOAEL to estimate a chronic NOAEL and deficiencies in the toxicity database; and special FQPA safety factors used to address residual concerns for children's health risks. The document provided only a limited discussion of evidence considered in how the uncertainty factors might be applied in cumulative risk assessments.

OPP has developed the current document to provide a more expansive discussion of the use of uncertainty and safety factors in the context of cumulative risk assessment and to restructure its presentation to follow more closely the framework and terminology presented in the FQPA safety factor guidance for individual chemicals (USEPA 2002a). This document also draws on definitions contained in the Cumulative Risk Assessment Guidance, which has been revised and issued (USEPA 2002b).

As explained in the FQPA safety factor guidance for individual chemicals (USEPA 2002a), OPP believes that it is critical to the protection of infants and children that it not rely on and not apply a default value or presumption in making decisions under Section 408 where reliable data are available that support use of a different safety factor in the assessment of risk. Use of the default value may result in an under- or overstatement of risk. OPP's reasoning applies with even more force in the context of cumulative risk assessments due to the additional complexities involved. Accordingly, for cumulative risk assessments, OPP also intends to make specific case-by-case determinations as to the size of the additional FQPA safety factor rather than rely on the 10X FQPA default value if reliable data permit. Further, as explained below, this individualized determination may involve application of FQPA safety factors to both the individual chemical members as well as to the entire cumulative assessment group (referred to as the "CAG") of common mechanism chemicals. This guidance document focuses primarily on the considerations relevant to determining a safety factor "different" from the default 10X that protects the safety of infants and children. Discussions in this document that reference decisions on applying an FQPA safety factor or the appropriateness, adequacy, need for, or size of such safety factor are premised on the assumption that reliable data would exist for choosing a "different" factor than the FQPA 10X default value.

II. Key Differences Between Single Chemical Risk Assessments and Cumulative Risk Assessments Relevant to Application of Standard/Traditional Uncertainty Factors and the FQPA Safety Factors

Although the FQPA Safety Factor Guidance for an individual chemical contains principles and concepts that are applicable to cumulative risk assessment, the difference in the objective of these two very different types of assessment must be kept in mind when considering the standard inter- and intraspecies uncertainty factors and the FQPA safety factor (including the traditional uncertainty factors that address deficiencies in the toxicity database and special FQPA safety factor components of the FQPA safety factor).

The key objective of a single chemical assessment is to identify all the potential toxicities that might be associated with each pathway of exposure, and to select the most sensitive critical effect to establish a reference dose (RfD) or a margin of exposure (MOE). In contrast to the single chemical risk assessment, a cumulative risk assessment does not focus on any effect that occurs at the lowest dose, but rather on a common effect that arises among a group of chemicals that act by a common mechanism of toxicity. Because a common mechanism of toxicity must be identified prior to conducting a cumulative risk assessment, these assessments by nature will tend to be based on a more extensive and robust database. Thus, there may be less of a need for uncertainty or safety factors to address database deficiencies. Furthermore, risk assessors should not automatically use chemical-specific RfDs when estimating the joint risk for the common mechanism group because these RfDs may be based on endpoints not pertaining to the common mechanism of toxicity. In a cumulative hazard

assessment, endpoints are identified that are common to the group and relevant to the common mechanism of toxicity.

There are two key aspects in the dose-response assessment for a cumulative risk assessment that differ from a single chemical assessment. First, unlike a single chemical assessment, a cumulative risk assessment requires a determination of the relative toxic strength or potency of each chemical member of the cumulative risk group so that the relative toxic contribution of each member can be determined. Second, although determining a point of departure (POD)[1] for estimating potential human risk is an integral part of both a single chemical and cumulative risk assessment, the POD for a cumulative risk assessment is based on an index chemical's endpoint pertaining to the common mechanism and is representative of the chemical group as a whole. The index chemical should be well defined toxicologically and have a high quality database. Although a chemical-specific adjustment may be made to derive an individual chemical's relative potency (e.g., application of a traditional uncertainty factor because a No-Observed-Adverse-Effect-Level (NOAEL) was not identified for the critical effect), it is important to emphasize that a common mechanism group of chemicals is considered to be a single unit in a cumulative risk assessment. Therefore, decisions on uncertainty or safety factors for the cumulative assessment group should reflect considerations on the complete set of chemicals **and** the common mechanism of toxicity. The approach for applying uncertainty factors and the FQPA safety factor is described in more detail below.

III. Analytical Framework for the Consideration of the Standard/Traditional Uncertainty Factors and the FQPA Safety Factor in Cumulative Risk Assessment

As part of a cumulative risk assessment, the risk assessor should address both the standard uncertainty factors (i.e., the intra- and interspecies uncertainty factor) and the FQPA safety factor (including the traditional uncertainty factors used to address deficiencies in the toxicity database and the special FQPA safety factor). Each of these factors is discussed below. The risk assessor should address both the size of such factors and how such factors are incorporated into the cumulative risk assessment.

A. The Standard Uncertainty Factors

In a single pesticide risk assessment, OPP would generally apply an intraspecies uncertainty factor (typically 10X) and an interspecies uncertainty factor (typically 10X) in

[1]A point of departure (POD) is a dose that can be considered to be in the range of observed responses, without significant extrapolation. A POD can be a data point or an estimated point that is derived from observed dose-response data. A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures.

such a manner as to ensure that this combined default 100X defined, at a minimum, the overall acceptable exposure. In a cumulative risk assessment involving several pesticides, OPP believes that the intra- and interspecies combined 100-fold default factor logically should be applied in a similar manner to account for potential human variability and to account for uncertainty in extrapolating experimental animal data to estimate potential human risk. Cumulative assessments, like single pesticide assessments, generally rely on animal data. Because a risk extrapolation from animal data to the human population is based on a common mechanism effect and thus is common to the whole group of pesticides, the uncertainty factors tied to the intra- and interspecies extrapolation should apply to the whole group. The point of departure (e.g., NOAEL or Benchmark Dose) for the index chemical is used to calculate route-specific margin of exposures (MOEs[2]) for the CAG. Generally, the expression of risk from the CAG can be expressed as the resulting MOEs which provide an indication of the extent to which anticipated exposure approaches a level that may produce adverse effects. The standard uncertainty factors should be used as a guide to evaluate the acceptability of the MOEs (excluding consideration of the FQPA safety factor) determined in a cumulative risk assessment.

The size of the standard intra- and interspecies uncertainty factors deemed adequate to protect infants and children will depend on the weight-of-the-evidence for a particular common mechanism of toxicity. Various authors have evaluated the intraspecies uncertainty factor using data from animal or human studies, as summarized by Dourson et al. (1996). On the whole, OPP interprets these evaluations along with statements in the 1993 National Research Council report *Pesticides in the Diets of Infants and Children* (NRC 1993) as meaning that for most chemicals the very large majority of people, including children, respond sufficiently similarly so that the tenfold intraspecies uncertainty factor is adequate to cover any variability that may exist in the human population. At the same time, there are chemicals for which some humans may display a greater range of variability and sometimes that variability appears age-related, with children exhibiting a greater degree of sensitivity than adults. The adequacy of the standard intraspecies factor to address the potential for greater sensitivity or susceptibility of children should be considered in the context of evidence on potential pre- and postnatal toxicity associated with the common mechanism of toxicity as discussed below.

As mentioned earlier, for interspecies variability, a factor of 10-fold is applied as a default assumption to account for differences in sensitivity between species when animal data are used to assess human risk. Although the default 10X is generally used in the Agency, when data indicate that humans are less or more sensitive than animals, the interspecies group uncertainty factor of 10-fold may be reduced or raised. For example, the Agency policy for rat thyroid disruption as a mechanism that leads to

[2]The margin of exposure is the point of departure divided by the anticipated or actual measure of human exposure.

follicular cell cancer is that a factor of unity is used instead of the traditional 10-fold factor because available data indicate that humans are less sensitive compared to rats to this mechanism of carcinogenesis (USEPA 1998). Therefore, when available, toxicokinetic and mechanistic data may be used for the application of data-derived uncertainty factors to account for both inter- and intraspecies differences. The World Health Organization International Programme for Chemical Safety recently developed guidance for risk assessors on the use of quantitative toxicokinetic and toxicodynamic data to address interspecies and interindividual differences in dose/ concentration-response assessment (WHO 2001).

B. The FQPA Safety Factor

In applying the FQPA safety factor provision, OPP must either retain the default FQPA safety factor or assign a different FQPA safety factor based on reliable data showing such factor is safe. If the default FQPA safety factor is retained, the risk assessor should incorporate the FQPA safety factor in the same manner as the traditional uncertainty factors as they relate to the group as a whole or to specific chemical members. A more complex process is called for if a different FQPA safety is chosen.

The FQPA safety factor provision is intended "to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." Thus, this guidance for the application of the FQPA safety factor provision, as it relates to determining the safety of a factor different from the 10X default FQPA safety factor, directs scientists in performing cumulative risk assessments to consider a three part framework that focuses on each of these elements:

- ❑ the completeness of the toxicity database;
- ❑ the potential for pre- or postnatal toxicity in infants and children; and ❑ the completeness of the exposure database.

In addressing these three areas, the FQPA safety factor analysis for cumulative risk assessment should focus on providing protection from the common toxic effect that could result from all pertinent routes and pathways of exposure to the members of the group that share the common mechanism of toxicity. Thus, the assessment of the uncertainty and safety factors, in the context of a cumulative risk assessment, has a more narrow toxicological focus than an individual assessment. As to exposure, however, a cumulative assessment has a much larger set of potential exposure scenarios, given the potential for multiple chemical exposures depending on the number of chemicals in the CAG and their respective uses.

1. Completeness of the Toxicity Database

In conducting cumulative risk assessments, OPP anticipates that it may apply

traditional uncertainty factors either to specific chemicals or to the entire chemical group or to both. In evaluating whether reliable data show a safety factor to be protective of infants and children when assessing cumulative risk, the risk assessor should consider the adequacy of safety factors to protect infants and children from uncertainty raised by database completeness issues both with regard to specific chemical members and to the entire chemical group. For cumulative risk assessment, evaluation of database completeness should focus on the completeness of particular toxicity databases as they pertain to the common mechanism of toxicity.

- ❑ **Traditional Uncertainty Factors Applied to An Individual Chemical Member of the CAG:** Uncertainty factors may occasionally be used in the determination of the Relative Potency Factors (RPFs) for a member of the cumulative risk assessment group (CAG) when there are limitations in its toxicity database. In a cumulative risk assessment, OPP establishes an RPF for each chemical based on the effect that they share in common and that pertains to their common mechanism of toxicity. The RPFs are used to estimate the toxicologically equivalent dose of each chemical member in the CAG compared to a reference or index chemical. This allows OPP to convert exposure attributable to one member of the group into toxicologically equivalent exposure to the index member of the group. Generally, OPP expects to have a very robust database that permits direct and uniform quantitative comparisons of the toxicity of different chemicals in studies conducted using comparable methodology. Furthermore, an index compound is selected based on it being well defined toxicologically for the common mechanism. Given that the index chemical will typically have a high quality database, it is anticipated that it will be rare to apply a database uncertainty to adjust its relative toxic potency or its point of departure.

  When OPP lacks data to make direct and uniform comparisons of toxicity across certain members of the CAG, the risk assessor may need to apply techniques to estimate comparable values. An example might involve an RPF analysis based on the comparison of the chemicals NOAELs for the common toxic effect. If there were no NOAEL established for one of the chemicals in the CAG, OPP might estimate the NOAEL for that chemical by applying an uncertainty factor to the LOAEL for that chemical (i.e., UF_L). In this example, the use of an uncertainty factor or adjustment factor would involve only a single chemical and would be determined by the unique characteristics of the specific chemical's database. Similarly, OPP might apply the subchronic to chronic uncertainty factor (UF_S) to adjust a toxicity value for an individual chemical, although use of this factor is expected to be rare because for most food-use pesticides OPP has an extensive chronic toxicity data set.

  The database uncertainty factor (i.e., $UF_{Dbchemical}$) may also be

applied to address missing studies that pertain to specific chemical members concerning the characterization of the common mechanism effects. For example, if data on effects in the young pertaining to the common mechanism were available for some members but not all, and those effects appear to be the most sensitive endpoint, then a database uncertainty factor may be applied to adjust specific chemical members RPF values to account for the absence of such data. The risk assessor should refer to the document for single chemical assessments, titled *Determination of the Appropriate FQPA Safety Factor(s) For Use in the Tolerance-Setting Process* (USEPA 2002a), for general guidance on determining the need for and size of the traditional database deficiency factor.

❑ **Traditional Uncertainty Factors Applied to the Cumulative Risk Group:** In addition to considering the need for uncertainty factors to address data limitations or deficiencies for individual chemical members of the CAG, the risk assessor should also consider whether there are deficiencies in the toxicity database that apply to the group of chemicals as a whole. This analysis involves answering the question whether it may be likely that the members of the CAG cause another critical effect produced by the identified mechanism of toxicity and whether such a critical effect would occur at a dose significantly lower than the doses used to calculate the relative potency factors or the Point of Departure currently being used. Thus, if the available information indicates that the CAG chemicals may have a substantially lower critical effect that raises concern for the young than predicted by existing toxicity data, it may be appropriate to apply a database uncertainty factor to the group (i.e., UF_{DbCAG}) until such time as additional testing is conducted to evaluate that potential. These decisions should be made on a case-by-case basis, taking into account the weight-of-the-evidence in the existing toxicity database in the context of the common mechanism of toxicity and how it pertains to susceptibility of the young.

The absence of data that pertains to the common mechanism of toxicity does not automatically warrant the application of a database uncertainty or safety factor. When data deficiencies exist pertaining to the common mechanism of toxicity, the risk assessor should consider the general, overall value of the missing study to the cumulative risk assessment. This includes consideration of how likely the effects measured in the study are to be the most sensitive toxic endpoint on which the estimation of cumulative risk should be based. Characterization of effects on the young and the analysis of data gaps should evaluate the overall value of the missing study to the cumulative risk assessment process for the common mechanism of toxicity. In addition to identification of toxicity information that is lacking that pertains to the common

mechanism of toxicity, review of the available data may also provide information as to the potential to detect effects that may significantly impact the cumulative risk assessment. In deciding the need for application of a database uncertainty factor to account for missing studies common to the CAG as a whole, the risk assessor should evaluate how thorough the testing is with respect to life stage assessment, endpoint assessment, and route and duration of exposure. It should be emphasized that studies using adult animals may help inform the judgment about potential effects in the young and the need for additional studies. Finally, it is important to avoid applying an uncertainty factor twice-i.e., to specific individual chemical members as well as a group factor to account for the same deficiency in the toxicity database.

2. Potential Pre- and Postnatal Toxicity

In assessing the FQPA safety factor, the potential for fetuses, infants, or children to be more sensitive than adults to toxic effects caused by the common mechanism of toxicity must be examined. The consideration of potential increased susceptibility would generally follow the same approach as used for individual chemicals, except that the focus is confined to the common toxic effect(s) produced by members of the cumulative assessment group (CAG). Thus, this decision is made regarding the group as a whole and not for individual members of the CAG.

The risk assessor should evaluate on a case-by-case basis the potential pre- and postnatal toxicity resulting from the common mechanism of toxicity only, taking into account all pertinent information. First, OPP would evaluate whether the toxicity data show a difference in the susceptibility of adults and the young to the specific toxic effects under review. As explained for individual chemicals, increased susceptibility can manifest as increased incidence, earlier outset, slower recovery, or increased severity of response in the young compared with adults.

If data on the common mechanism of toxicity indicate differential pre- or postnatal toxicity, the risk assessor should then consider whether the available information indicates a significant level of concern for such effects. As described in the FQPA safety factor guidance, the risk assessor should consider several factors or lines of evidence that would either increase or decrease the concern for potential pre- or postnatal toxicity in humans. These factors include criteria relating to the type of pre- and postnatal toxicity observed, the nature of the dose-response, information on toxicokinetics, and data on mode of action. If there is evidence of a high degree of concern for the CAG chemicals, the risk assessor should evaluate whether the standard approach of applying traditional uncertainty factors to the relative potency factors or the Point of Departure for the Index Chemical provides assurance that infants and children will be adequately protected.

It should be emphasized that OPP does not believe that the safety of infants and

children requires retention of a special additional safety factor for a group of pesticides that share a common mechanism of toxicity whenever the common toxic effect involves some increased susceptibility of the young. Risk assessors should focus on the degree of concern and the residual uncertainties raised by increased susceptibility in evaluating what safety factor would be protective of infants and children. In addition, risk assessors are reminded that a recommendation with respect to the need for a special safety factor due to potential pre- or postnatal toxicity of the CAG should be made for the CAG as a whole and should not be predetermined based on whether OPP separately decided that one or more individual members of the CAG warranted an additional factor for potential pre- or postnatal toxicity. This is because a cumulative risk assessment is conducted on the basis that the CAG induces a common effect by a common mechanism. Thus, it would not be appropriate to apply a special FQPA safety factor because a small subset of the CAG has been shown to induce effects in infants and the young. Additional guidance on determining the degree of concern and residual uncertainties associated with observed susceptibility in the young can be found in the OPP's revised policy document for individual chemical assessments, titled *Determination of the Appropriate FQPA Safety Factor(s) For Use in the Tolerance-Setting Process* (USEPA 2002a).

3. Adequacy of the Exposure Database

As with aggregate exposure assessments, the exposure database for a cumulative risk assessment should be considered adequate if the risk assessor is confident that the exposure estimate did not understate the potential exposure. Any consideration of the exposure estimate should take into account both the inputs used in the assessment and the methods for combining exposure to produce the cumulative risk assessment.

With respect to inputs, the risk assessor should consider whether the cumulative risk assessment encompasses all potentially significant sources of exposure. For example, the risk assessor may choose to exclude from the quantitative estimate of food exposure for the Cumulative Assessment Group certain chemical-crop combinations for which it lacks monitoring data. The risk assessor should evaluate the potential significance of any excluded exposure scenario, taking into account not only the magnitude of the potential exposure but also the relative toxicity of the chemical(s) involved. For example, if OPP has no monitoring data on the levels of a relatively less toxic pesticide in almonds, the omission of an estimate of potential exposure is not particularly likely to influence the magnitude of the overall cumulative risk assessment because almonds are only a small fraction of the diets of people who consume them.

The risk assessor should also consider whether, in the absence of more accurate, chemical-specific information, the cumulative exposure assessment used generic data to produce a conservative estimate of potential exposure. Given the available databases, this is more likely to occur when estimating exposure from the drinking water and residential pathways. Although OPP will use the best available information to develop region-specific estimates from drinking water and residential use, in some cases, OPP uses an input value derived from a generic database or based on scientific judgment to calculate exposure for a particular exposure scenario. For example, OPP recognizes that the level of pesticide residues in surface water will vary geographically, depending on the extent of pesticide use and local site vulnerability to runoff, among other factors. To the extent that OPP chooses to estimate drinking water exposure using residue levels expected around a vulnerable, heavily treated site, such estimates would overstate exposure to people in other parts of the region. Similarly, estimates of residential exposure developed using the Residential Standard Operating Procedures tend to describe the high-end or upper-bound of potential exposure and do not take into account variability in use patterns from region to region. Thus, to the extent that such “conservative” exposures constitute a significant portion of the overall cumulative exposure assessment, the resulting estimate would be less likely to understate potential risk.

In addition, the likelihood that a cumulative risk assessment will (or will not) understate potential exposure depends, in part, on the method used to combine exposure estimates for different pathways. In a screening level assessment of cumulative risk, OPP may combine different, deterministic high-end values from different pathways, thereby producing an estimate that is at or above the upper-bound of exposure. Such an assessment would describe the exposure encountered in the unlikely event that an individual received simultaneously both high-end food, water, and residential exposure. In practice, such exposure scenarios would probably never occur, or would only occur rarely. Conversely, if exposures by different pathways have been combined using probabilistic techniques, the additional conservativism would be decreased.

Because of the complexity of cumulative exposure assessments, the

consideration of the completeness of the exposure database cannot be reduced to a simple set of guiding principles. Rather, the consideration of the appropriateness or adequacy of any additional uncertainty factor should be made on a case-by-case basis taking into account all of the aspects of the assessment which may tend to underestimate potential exposure and those which may tend to overestimate potential exposure. To the extent possible, the risk assessors should attempt to conduct sensitivity analyses using alternative assumptions to evaluate the potential significance of different assumptions. Ultimately, however, the risk assessors should provide a characterization of the exposure assessment-its strengths and weaknesses, as well as the potential for over- or underestimation of exposure-and make a recommendation about the adequacy of a different safety factor to protect the safety of infants and children.

The manner of incorporating uncertainty or safety factors in a cumulative assessment to account for hazard and exposure uncertainties or deficiencies is generally summarized in the following Table (1):

IV. Decisionmaking Process-Integration of the Consideration of the Adequacy of the Toxicity and Exposure Databases and the Potential for Pre- and Postnatal Toxicity

Although important aspects of the FQPA safety factor analysis occur in the toxicity and exposure assessments for the cumulative risk assessment, ultimately, decisions on safety factors should be made in the risk characterization stage. In the risk characterization stage, the risk assessor should attempt to integrate the information and analysis described above. In addition, the risk characterization section may address other aspects of the risk assessment methodology that could contribute to the conservativeness of the assessment (e.g., the percentile of exposure considered reliable for estimating potential risks). The risk assessor should describe the overall strengths and weaknesses of the assessment that would be relevant to the consideration of the FQPA safety factor. The risk assessors should develop a recommendation with respect to the standard/traditional uncertainty factors and the FQPA safety factor that takes the full range of information into account.

Table 1. Incorporation of Uncertainty/Safety Factors in Cumulative Risk Assessment	
Factors Applied to Specific Chemical Members of the Cumulative Assessment Group (CAG)	
LOAEL to NOAEL (UF_L)	≤10-fold factor is used to estimate a NOAEL from a LOAEL for a specific chemical's relative toxic potency factor.
Subchronic to Chronic (UF_S)	≤10-fold factor is used to estimate a chronic point of departure from a study of less than chronic treatment duration for a specific chemical's relative toxic potency factor.
Deficiencies in the Toxicity Database ($UF_{Db\ chemical}$)	≤10-fold factor is used to address database deficiencies, which are not addressed by UF_L and UF_S factors, in estimating the relative toxic potency of each chemical member of the CAG.
Factors Applied to the Cumulative Assessment Group After Conducting Cumulative Risk	
Human Variation (or intraspecies) (UF_H)	≤10-fold UF intended to account for potential variation in sensitivity among humans and is considered to include toxicokinetic/dynamic processes.
Experimental Animal to Human (interspecies) (UF_A)	≤10-fold UF intended to account for uncertainty in extrapolating data from laboratory animals to project human risk, considered to include toxicokinetic/dynamic processes.
Deficiencies in the Toxicity Database ($UF_{Db\ CAG}$)	≤10-fold factor is used to address database deficiencies that are common to the CAG.
Special FQPA Safety Factor	The reasons for such a factor include: concern about pre- or postnatal toxicity and deficiencies in the exposure database. It is anticipated that most toxicity database issues will be dealt with on the individual chemical members before conducting the cumulative assessment. The risk assessor should not account for the same deficiency twice. Consideration should be given to whether these concerns pertain to the common toxic effect and common mechanism of toxicity.

References

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