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**THE OFFICE OF PESTICIDE PROGRAMS' POLICY
ON
DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S)
FOR USE IN THE TOLERANCE-SETTING PROCESS**

**OFFICE OF PESTICIDE PROGRAMS
U.S. ENVIRONMENTAL PROTECTION AGENCY**

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DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) FOR USE IN THE TOLERANCE-SETTING PROCESS

I. EXECUTIVE SUMMARY

On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law. Effective on signature, FQPA significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). Among other changes, FQPA established a stringent health-based standard (“a reasonable certainty of no harm”) for pesticide residues in food to assure protection from unacceptable pesticide exposures. The new law also provided heightened protections for infants and children. Specifically, it directed EPA to use an additional tenfold margin of safety in assessing the risks to infants and children, to take into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases. The statute authorized EPA to replace this default 10X “FQPA Safety Factor” with a different factor only if, based on reliable data, the resulting margin would be safe for infants and children.

Because of the critical importance of assuring adequate protection of infants and children, EPA established an intra-agency Task Force of senior staff, knowledgeable in the fields of hazard and exposure assessment, to identify the types of information that would be appropriate for evaluating the safety of pesticides to infants and children. The Task Force included representatives from the Office of Prevention, Pesticides and Toxic Substances, the Office of Research and Development, the Office of Children’s Health Protection, the Office of Water, and the Office of Solid Waste and Emergency Response. The two Task Force reports contained many useful recommendations considered by the Office of Pesticide Programs in the development of this guidance document.

This document describes the Office of Pesticide Programs’ (OPP) policies for determining the appropriate Food Quality Protection Act (FQPA) Safety Factor(s) to apply when establishing, modifying, leaving in effect or revoking a tolerance or exemption for a food use pesticide. It presents the legal framework for the FQPA Safety Factor and key interpretations of that framework. It states that, while the legislative language incorporates the term “safety factor” instead of the term “uncertainty factor,” OPP believes that Congress clearly intended the FQPA Safety Factor to address uncertainty resulting from incompleteness of data and, therefore, deems the statutory term to incorporate the “uncertainty factor” concept. The document offers the opinion that the FQPA Safety Factor is to be applied in addition to the two routine or baseline uncertainty factors which account for 1) differences in sensitivity and variability between humans (the “intraspecies” uncertainty factor) and 2) differences in sensitivity between experimental animals and humans, if animal data have been used as the basis for deriving the hazard values (the “interspecies” uncertainty factor). Therefore, the FQPA Safety Factor would include other uncertainty or modifying factors used in the calculation of hazard values, for example, the database uncertainty factor that is applied when one or more critical core studies are missing.

The document describes the universe of pesticides for which FQPA Safety Factor determinations would be made primarily as food-use chemicals of “conventional” chemistry for which hazard values such as the acute or chronic reference doses (RfD) can be derived. OPP would expect to make FQPA Safety Factor decisions when assessing risk to infants and children up through the time of sexual maturation, women of child-bearing age, and on occasion, sexually mature males. FQPA Safety Factor recommendations will occur as the risk characterization is being developed; the final decision will be made during the risk management process. .

The guidance describes the criteria by which OPP determines the completeness of the toxicology database for conducting a high quality hazard characterization. OPP makes this determination employing a weight-of-the-evidence (WOE) approach. The core toxicology database for a specific chemical generally consists of studies which meet three criteria: 1) All studies in the core database must have “official” testing guidelines or standard, well-documented protocols available; 2) They will have been required under FIFRA/ FFDCA as first tier requirements or triggered by the results of Tier 1 or other existing studies (see the regulations in 40 CFR 158.340 “Subpart F”) or under a well-established policy and practice for registration and reregistration/renewal (e.g., data call-ins) and this requirement has resulted in the generation and submission of the data with which the Agency has acquired experience in evaluating; and, 3) There is consensus in the scientific community that there is a body of evidence supporting the conclusion that the results of such studies improve in a significant way the understanding of the potential hazard of the pesticide to humans, including infants and children.

The document notes that OPP will, in the next few months, propose to revise the toxicology data requirements in Part 158, to include several new studies as Tier 1 requirements (e.g., the acute and subchronic neurotoxicity studies in adult mammals, the developmental neurotoxicity study, two immunotoxicity studies, and the 21-day dermal study) plus others as Tier 2 (i.e., conditionally required). In addition, there is a description of the criteria and other bases by which OPP has concluded that it is appropriate to begin the process to issue data call-ins for the acute and subchronic neurotoxicity studies in adult mammals and the developmental neurotoxicity study for a subset of conventional chemistry pesticides which are known neurotoxins.

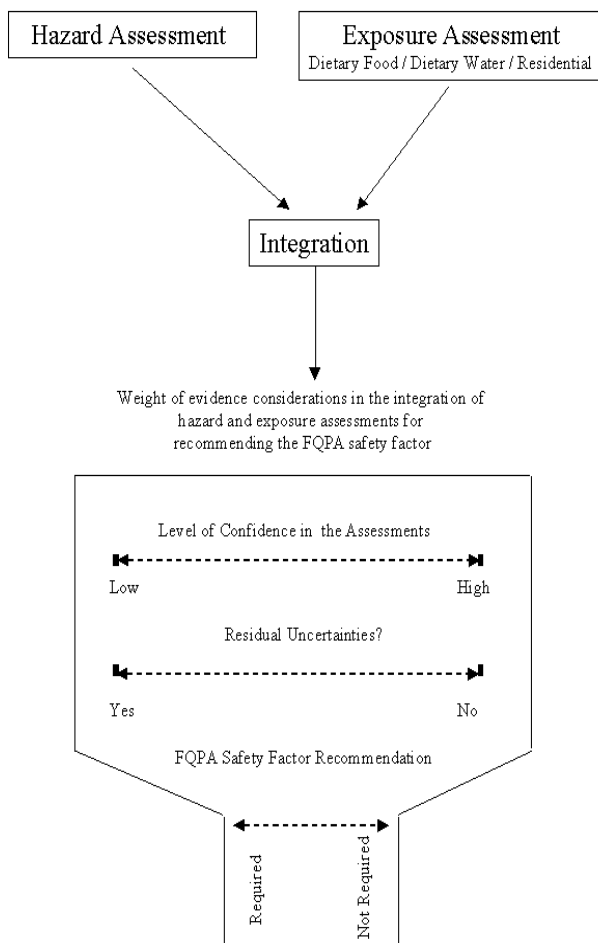
The practice of application of a database uncertainty factor when critical core studies are missing or inadequate is described, including the expectation that the number of studies considered critical for a “high confidence” chronic reference dose will be expanded in the near term from five to six, and, then, after the studies are routinely required, received and understood, to eight. The database uncertainty factor fulfills the same purpose as, and, in effect, becomes part of the FQPA Safety Factor.

This guidance document incorporates the criteria and factors for assessing the degree of concern regarding the potential for pre- and postnatal effects, as presented in the framework described in the report of the Toxicology Working Group of the Agency 10X Task Force entitled “Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children’s Health.” (Toxicology Working Group, 1999).

It also considers the completeness of the toxicology database and degree of concern in the selection and application of uncertainty factors when calculating the acute or chronic RfD and in the recommendations regarding the FQPA Safety Factor. The RfD derivation process takes into account deficiencies in the core toxicology database and the potential for hazard to fetuses, infants and children (and, therefore, the degree of concern). This paper articulates criteria for determining OPP's overall level of confidence in the hazard-related information and hazard assessment approaches employed. If, for some reason, an assessment does not meet this standard, then the assessment is said to contain "residual uncertainties or concerns." Any residual concerns remaining after the hazard assessment is examined are dealt with when making the final FQPA Safety Factor decision(s). During the period after a determination is made to require new toxicology studies, but before they become part of the core toxicology database, their absence is evaluated as part of "residual uncertainties or concern" in the FQPA Safety Factor assessment process. This document states OPP's intention to solicit broad public input regarding the appropriate consideration of the absence of these particular newly-required studies in the FQPA Safety Factor assessment process.

Just as for hazard potential, determination of the completeness of the exposure database-in the context of aggregate exposure and risk assessment-is a primary consideration relative to the FQPA Safety Factor. As described in the report of the Exposure Working Group of the Agency 10X Task Force entitled "Exposure Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health" (Exposure Working Group, 1999), OPP estimates exposure using chemical-specific and other reliable empirical data as well as models and conservative assumptions, which also are based upon reliable data. The Office is confident that, in the great majority of cases, it is not underestimating exposure to infants and children or to the general population. The guidance document acknowledges the desirability of obtaining more extensive and specific exposure data and notes that OPP continues to pursue the acquisition of such data from the private sector and its own and other agencies' research efforts. If any residual concerns remain after the exposure assessment is examined, these are dealt with when making the final FQPA Safety Factor decision(s). The guidance states that the absence of detailed and specific exposure data would require the application of an additional safety factor unless OPP can determine that the available data and its assessment methodologies give a high degree of confidence that exposure to infants and children is not underestimated. However, because OPP's approach to estimating exposure in the absence of extensive, specific data is typically very conservative, OPP can usually conclude, with a high degree of confidence, that its approach adequately protects infants and children, and the FQPA Safety Factor would not be needed to address uncertainties in the exposure database.

CONSIDERATIONS IN THE FQPA SAFETY FACTOR RECOMMENDATION PROCESS



The guidance document notes that the decision, either that the default FQPA Safety Factor is to be applied or that there are reliable data which support the application of a different factor, uses a “weight-of-the-evidence” (WOE) approach. This approach simply means that all of the data with regard to both hazard and exposure are considered simultaneously as the total body of evidence with regard to the pesticide(s) being evaluated. The integration approach to evaluating the available hazard- and exposure-related information involves characterization of the overall confidence that infants and children will be protected. As illustrated in the figure, the weight-of-the-evidence considerations include the level of confidence in the hazard and exposure assessments, and whether or not there are any residual uncertainties identified in the risk characterization. If there is a high level of confidence that the combination of the hazard and exposure assessments is adequately protective of infants and children, then the default FQPA factor would not be applied at this stage in the process.

For example, the optimal case would

be one in which there is a high level of confidence that the hazard and exposure assessments are sufficiently conservative and there are no residual uncertainties in the assessment; then it would not be necessary to apply an additional safety factor to protect infants and children. At the other extreme is the case where OPP may find that reliable data do not support a particular finding other than to retain the 10X default factor, given the low level of confidence that the hazard and exposure assessments are sufficiently conservative and there are residual uncertainties that have not been dealt with in the assessment. Alternatively, in other cases where there is also a low level of confidence in the hazard and exposure assessments and residual concerns remain, an additional safety factor other than the 10X default (perhaps even greater) would be applied. The size of the final factor would depend on the overall weight-of-the-evidence and the level of confidence in the assessment.

The recommendation concerning the FQPA factor is made based upon consideration of the nature and level of confidence in the hazard and exposure assessments, the degree of concern for potential hazard to the fetus, infants and children, and any residual uncertainties that are not accounted for in the hazard and exposure assessments. The final decision on the FQPA Factor is informed by the science presented in the risk characterization and the recommendation.

II. PURPOSE OF THIS DOCUMENT AND INTRODUCTION

The purpose of this document is to describe the policies employed by the Office of Pesticide Programs in making a determination regarding the FQPA Safety Factor when developing aggregate risk assessments and regulatory decisions for single active ingredient pesticides. In the future, as the 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 groups of chemicals sharing a common mechanism of toxicity.

This version of the policy has been written in light of review and comment offered by the FIFRA Scientific Advisory Panel (SAP) on several earlier versions over the last two and a half years, comments by other external parties offered in the context of these SAP meetings, and the reports of the Toxicology and Exposure Working Groups of the Agency 10X Task Force. The Agency 10X Task Force was established in March, 1998, to assist in addressing the general considerations regarding the use of the ten-fold margin of safety for infants and children provided for in the FQPA. The Task Force formed a Toxicology Working Group and an Exposure Working Group. Working Group members included representatives from EPA's Offices of Prevention, Pesticides and Toxic Substances, Research and Development, and Children's Health Protection as well as other Agency offices with an interest in the issue. A representative from the U.S. Department of Agriculture participated in the Exposure Working Group.

The approach set forth in this document will be subjected to public notice and comment in accordance with the processes suggested by the Tolerance Reassessment Advisory Committee. It also will be discussed at the May, 1999, meeting of the FIFRA Scientific Advisory Panel. The guidance document then will be revised, as appropriate, and issued later this year.

III. LEGAL FRAMEWORK

A. Statutory Provision on the FQPA Safety Factor

The Food Quality Protection Act (FQPA) of 1996 (Pub. L.104-170) was signed into law on August 3, 1996. FQPA establishes a new safety standard and new procedures for EPA's pesticide tolerance-setting activities. Under new Section 408(b)(2)(A)(i) of FFDCA, EPA can establish, revise or leave in effect a tolerance (the legal limit for a pesticide chemical residue in or

on a food) only if it is determined to be "safe." Section 408(b)(2)(A)(ii) defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." Section 408(b)(2)(C) requires EPA to give special consideration to infants and children by ensuring "that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue."

The FQPA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects,...an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(c) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Threshold effects are those considered to have exposure doses at some identifiable level which are likely to be without appreciable risk of deleterious consequences. The shapes of the dose response curves for such effects would be expected to be non-linear. Both cancer and non-cancer effects may exhibit these properties.

(FQPA contains terms related to risk assessment that are outdated or inconsistent with the Agency's and OPP's current risk assessment vocabulary and practices. This document will use language that reflects current practice. For instance, the term "hazard" will be used instead of "toxicity" when used in combination with "assessment" or "characterization" to describe those phases of the risk assessment process.)

B. Key Interpretational Issues

1. Is there a difference between a safety factor and an uncertainty factor?

When regulatory agencies first adopted the approach of setting acceptable levels of exposure to potentially risky substances, those levels were usually derived by dividing the dose levels at which no adverse effects were seen in animal studies by "safety factors" designed to account for, among other things, differences between animals and humans and differences among humans (commonly referred to as the inter- and intraspecies factors). Because the factors cannot guarantee absolute safety and the factors are an attempt to address uncertainties in the knowledge base, more recently, EPA has begun using the term "uncertainty factors" instead of "safety factors."¹ Given that EPA has used both terms to address the same concept and Congress clearly

¹ EPA also uses the term "modifying factor" to describe another factor sometimes used in the derivation of the RfD. The "modifying factor," as EPA employs it, is applied when scientific uncertainties in the study chosen for derivation of the RfD are not explicitly addressed by one or more of the "uncertainty factors." OPP does not regard Congress' use of the term "safety factor"

intended the FQPA factor to cover uncertainty resulting from incompleteness of data, OPP does not read any substantive meaning into Congress' use of the phrase "safety factor" rather than "uncertainty factor." The equivalence in the use of the terms "safety factor" and "uncertainty factor" is further reflected in the legislative history where Congress both described the traditional inter- and intraspecies factors as "safety factors" and directed that the FQPA Safety Factor provision be interpreted in furtherance of the NRC/NAS recommendation for use of an additional "uncertainty factor" of up to 10X to protect infants and children (House report 104-669, 104th Congress, 2d Sess. 41, 43 (1996)).

Even though EPA more frequently uses the term "uncertainty factor," because the statute uses the term "safety factor," OPP will continue to use the term "safety factor" in referring to the additional FQPA factor for the protection of infants and children. Nevertheless, because this document discusses past OPP actions and Agency-wide policies, OPP often will also use the term "uncertainty factor" in this document.

2. What is the FQPA Safety Factor additional to?

Congress specified that the 10X factor should be an "additional" factor without stating in the statute what served as the baseline safety factor. Nonetheless, given existing risk assessment procedures, there can be little doubt as to Congress' intention. For almost 30 years, EPA, as well as others in the scientific and regulatory community, has routinely been using at least two ten-fold safety or uncertainty factors when relying on animal testing to assess the potential for human hazard posed by exposure to chemicals. The two ten-fold factors used most often are designed to address both the extrapolation of the results of animal studies to humans and variability and sensitivity within humans and to serve as the starting point for defining an acceptable exposure level for a chemical. Furthermore, it is also well-established regulatory practice to apply, on a case-by-case basis, "additional" safety, uncertainty, or modifying factors along with the baseline inter- and intra-species factors where the circumstances warrant such additional factors. These additional factors have been used principally to address gaps in the toxicology database or deficiencies in the key existing toxicology studies. For food use pesticides, it only infrequently has been found to be necessary to apply additional factors to account for gaps or deficiencies of this nature. OPP has traditionally not used safety or uncertainty factors to address exposure issues. Thus, consistent with OPP's past risk assessment and regulatory practices, OPP believes Congress intended that the additional FQPA Safety Factor be "in addition to" only the standard, baseline inter- and intra-species uncertainty factors.

3. What additional factors qualify as FQPA Safety Factors?

Not only does OPP's prior practice regarding use of the inter- and intra-species uncertainty factors provide the baseline to which the FQPA factor is added, but OPP's pre-FQPA use of additional uncertainty factors helps to provide content to the FQPA Safety Factor itself. It

as excluding the concept covered by the modifying factor.

is OPP's view that the additional FQPA Safety Factor codified, to a certain extent, OPP's pre-FQPA use of uncertainty factors in addition to the standard inter- and intra-species factors. For example, as noted, additional uncertainty or modifying factors have traditionally been used by OPP (and EPA) to address deficiencies in the toxicology database. This concept is reflected expressly in the FQPA Safety Factor provision by the direction that an additional 10X factor be applied, for among other reasons, "to take into account . . . completeness of the data with respect to . . . toxicity." Thus, it is clear that the pre-FQPA additional uncertainty factor to address a deficiency in the database concerning effects of concern for infants and children has become, after passage of the FQPA, an additional FQPA Safety Factor. OPP believes it is unreasonable to assume that when Congress specified an "additional" safety factor "to take into account . . . completeness of the data with respect to . . . toxicity" it intended that OPP apply its traditional database uncertainty factor where a study was missing or inadequate and then apply a second safety factor under the FQPA for the same deficiency.

The FQPA Safety Factor provision, however, was not simply a codification of existing practice. It was both a codification and an expansion. Prior to the enactment of the FQPA, OPP already considered both the observed adverse effects shown in studies and the completeness of the toxicology database in determining the appropriate composite uncertainty factor to be applied in calculating the RfD. It was only on rare occasions, however, that OPP found that an additional factor was needed because either the adverse effects were so severe or other substantive results raised sufficient questions regarding the adequacy of the traditional uncertainty factors.² Congress, by specifically including a reference to potential pre- and postnatal toxicity as a factor justifying an additional 10X factor for pesticides, has effectively expanded OPP's pre-FQPA practice concerning the role substantive study results play in safety factor determination by placing increased emphasis on potential pre- and postnatal toxicity. (An explanation of how OPP will account for pre- and postnatal toxicity in the hazard and risk characterization phases of risk assessment will be discussed in Section V.)

An additional expansion of pre-FQPA practice was effected by Congressional reference to the completeness of the exposure database. Prior to the enactment of FQPA, OPP did not use an express safety/uncertainty factor approach with exposure assessments. That is, OPP did not modify exposure assessments by some factor to address inadequacies in the exposure database. Rather, OPP attempted to ensure that exposure was not underestimated by using reasonable high-end exposure assumptions where empirical exposure information was unavailable. As with pre- and postnatal toxicity, Congress, by explicitly referencing the completeness of the exposure database as one of the considerations justifying an additional 10X factor, has placed new emphasis on the need to ensure that exposure assessments are based upon complete information relevant to infants and children so that risks are not underestimated. (An explanation of how OPP will

² Contrary to statements in the NRC Report entitled "Pesticides in the Diets of Infants and Children" (NRC,1993) (p.361), an additional 10X factor has not been automatically applied by OPP or EPA whenever a study identified fetal developmental effects.

account for completeness of the exposure database in the exposure assessment and risk characterization phases of risk assessment is discussed in Section VI.)

4. What Discretion Does EPA Have in the Application of the Additional FQPA Safety Factor?

The statute established a default position that OPP should apply an additional 10X safety factor as a default to account for pre- and postnatal toxicity and completeness of the toxicology and exposure databases. The statute also grants OPP the discretion to apply a different safety factor where reliable data show that such a factor will be safe for infants and children. Thus, OPP can either rely on the default 10X value or, in appropriate circumstances, determine that the data support a “different” factor that is protective of infants and children. When OPP finds that it has reliable data to set a different factor, OPP will base such different factor upon an in-depth analysis of the underlying databases and not some sort of arbitrary dividing-up of the 10X default value. OPP does not believe that Congress intended that the default 10X factor be split up using some mathematical formula between pre- and postnatal toxicity and the completeness of the toxicology and exposure databases. The in-depth analysis may result in a finding that a factor either greater or lesser than 10X should be added to the traditional inter- and intraspecies factors or that no additional factor in addition to the traditional factors is needed. It may also result in the conclusion that an additional factor of 10X is retained for the protection of infants and children because the data support the conclusion that the default value is the appropriate value.

Earlier OPP policy statements have described decisions regarding the additional FQPA Safety Factor as to whether to “retain, reduce, or remove” the 10X factor. This language was originally adopted by OPP to emphasize its position that the starting point in any assessment is that the FQPA 10X Safety Factor is assumed to be necessary to protect the safety of infants and children unless reliable data show otherwise. Although OPP continues to adhere to this core principle of the FQPA Safety Factor provision, OPP has dropped the “retain, reduce or remove” language. OPP has become concerned that this language contains an erroneous implication that would restrict implementation of the FQPA Safety Factor provision in a manner that is most protective of infants and children. The “retain, reduce or remove” language implies that OPP thought any “different” additional factor applied could be no greater than 10. The statute is not so limiting. In fact, the final safety factor could be greater than 10X.

5. What are reliable data?

OPP may use a margin of safety different from the default FQPA Safety Factor where OPP can conclude, based on “reliable data,” that the margin chosen will protect the safety of infants and children. Several provisions in FFDCA section 408 mention the need for reliability of data or information. (See, e.g., §§ 408(b)(2)(A)(ii), 408(b)(2)(D)(i).) OPP does not interpret the reliable data requirement in the infants and children’s provision as mandating that any specific

kind of data be available, just that the data and information that form the basis for the selection of a different safety factor must be sufficiently sound that it could routinely rely on such information in taking regulatory action.

In conducting both hazard and exposure assessments, OPP, at times, relies on a wide range of assumptions and models to evaluate and supplement specific data available on the pesticide. For example, almost all hazard assessments depend on the assumption that effects observed in animals can be used to predict both effects in humans and the level below which those effects are not likely to occur. Rarely does OPP have human testing data for a pesticide; however, more generic data and information concerning the relevance of animal testing to humans are sufficiently reliable to support these assumptions. An example in the area of exposure assessment is OPP's use of a tolerance value as the assumed level of pesticide residue in food. Although, in a number of circumstances, OPP has studies analyzing pesticide residue levels in food at the time of purchase or consumption by the consumer, there are many circumstances, particularly those involving most new pesticides, where OPP does not have such data. OPP generally does have data showing residue levels at the time of harvest, as well as more general information regarding what happens to residue levels over time and during food processing. Taken together, this information provides reliable data supporting OPP's assumption that using tolerance level values for residue levels will not understate exposure.

In examining whether empirical data used with assumptions or models provide reliable data that allow OPP to set a different margin of safety than the additional ten-fold default value for the protection of infants and children, OPP will focus on whether the assumption or model is based on reasonable scientific judgment that hazard or exposure, as applicable, will not be underestimated. To be reasonable, scientific judgment may not be based on mere speculation but must take into account relevant information and data. How much information and data, and how specific those data must be, will depend on the nature of the assumption. In some cases, only very general information or data will be needed. For example, in the absence of data on dermal absorption for a pesticide, OPP will often assume that the pesticide is one hundred percent absorbed. If such an assumption is made, the absence of the specific dermal absorption data would not mean that OPP does not have "reliable data" to make a finding on children's safety. Rather, basic scientific principles provide the reliable data to support the assumption that a human cannot absorb more than 100 percent of a substance to which he or she is exposed dermally. OPP can conclude that the assumption is a reasonable scientific judgment that ensures that children's exposure has not been underestimated for this route of exposure.

IV. OVERALL APPROACH TO THE FQPA SAFETY FACTOR

A. The Default 10X Safety Factor vs. a Different Safety Factor

As explained above, the statute established an additional 10X factor as a default value ~~or~~ but also gives OPP the discretion to apply a different margin of safety based on reliable data and an individualized assessment, on a case-by-case basis. FQPA requires that an additional 10X

factor be applied as a default where it cannot be shown on the basis of reliable hazard and exposure information and assessments that a different safety factor would maintain an adequate margin of safety for infants and children. Where reliable data are available, however, OPP has the discretion to choose between the default approach and an individualized assessment. OPP, as a policy matter, prefers not to simply apply a default value in making decisions under section 408 where reliable data are available that support an individualized determination. In OPP's view, the statute's prescription for use of a default additional 10X safety factor to address such varied, and potentially serious, concerns as potential pre- and postnatal toxicity, and the completeness of the toxicology and exposure databases is somewhat of a crude instrument. A pesticide may have weaknesses in its toxicology and exposure databases but indicate no concern for potential pre- or postnatal toxicity. Another pesticide might have a complete database that demonstrates that it does result in pre-natal toxicity. A third pesticide might have an incomplete database that, nonetheless, shows the potential for pre- and postnatal toxicity. Further, incomplete databases are not equally incomplete, and all pre- or postnatal toxicities are not of equal concern. Yet, if the 10X factor is applied as a default, each of these myriad variations would get exactly the same treatment. A 10X factor might overprotect in one instance but underprotect in the next. For example, prior to the passage of the FQPA, deficiencies in the hazard data alone, on occasion, prompted OPP to apply one or more additional factors of up to 10X.³ Conversely, where data deficiencies are minor and any pre- or postnatal toxicity identified is well characterized, use of an additional 10X factor may be unnecessary to protect infants and children.

For these reasons, where reliable data are available, OPP favors an approach that attempts to make a specific case-by-case determination as to the size of the additional factor rather than rely on the 10X default value. Determination of the magnitude of the additional factor would involve evaluating the completeness of the toxicology and exposure databases and the potential for pre- or postnatal toxicity. OPP believes that careful analysis of the completeness and quality of the existing databases should, in most instances, account for uncertainties including FQPA considerations such that OPP will not have to rely on the additional 10X value as a default. Individualized assessments may still result in the use of an "additional" factor of 10X. Alternatively, these assessments may result in "additional" factors greater or less than 10X, or no additional factor at all.

B. The Problem of Double-Counting

Certainly, the major focus of application of the statutory provision on the FQPA Safety Factor is to insure that infants and children are adequately protected from unsafe risks to conventional food-use pesticides. Nonetheless, care must be taken to avoid the "double-

³ These uncertainty factors cover three areas of deficiency: lack of good long-term dosing data, lack of a "good" NOAEL, and lack of other key data in the database needed to yield a high confidence hazard value (e.g., RfD). In addition, on one occasion, OPP incorporated an additional factor because the animal hazard data indicated a very high degree of concern for human health. [See further discussion below]

counting” of safety/uncertainty factors. Such double-counting could occur in one of two ways. First, given that the determination of the FQPA Safety Factor builds upon prior practice with regard to the application of additional uncertainty factors in the risk assessment process, double-counting could occur if the same concern was relied upon to justify both a traditional uncertainty factor and a separate FQPA Safety Factor. For example, when calculating an RfD, OPP may apply a database uncertainty factor where a key core study addressing potential hazard to infants and children is missing or inadequate. To apply a second uncertainty factor, under the aegis of the FQPA Safety Factor, to address the same completeness of data issue would be an unjustified doubling of additional safety/uncertainty factors. OPP believes that by making clear in this document that traditional additional uncertainty factors, such as the database uncertainty factor, serve as a part of the FQPA Safety Factor, there is less likelihood that such double-counting will occur.

Double-counting could also occur because FQPA Safety Factor issues are addressed at more than one stage in the risk assessment process. As described above, the specific concerns that led to the FQPA Safety Factor provision (potential pre- and postnatal toxicity and completeness of the toxicology and exposure databases) are primarily addressed in the hazard and exposure assessments. However, to the extent there are any residual uncertainties that have not been addressed by these assessments, these residual uncertainties are taken into account in the final stage of the risk characterization process. Double-counting in this several-stage process can be avoided, OPP believes, if at each stage of the risk assessment process, the risk assessors adequately document what decisions are being made and the reasons for those decisions.

C. The Process for Decision-making on the FQPA Safety Factor

If OPP determines that reliable data exist to depart from the default safety factor of 10 and to choose a different factor, decisions regarding the size of that factor will be made at three different stages in the risk assessment process. First, decisions regarding the now-codified uncertainty factor pertaining to the completeness of the toxicology database will continue to be made as part of the hazard assessment. The hazard assessment will also address any pre- or postnatal toxicity identified in the available data and take such hazard into account to the extent possible in calculating an RfD or a Margin of Exposure (MOE). Second, decisions regarding an additional uncertainty factor to account for deficiencies in the exposure database will be made as part of the exposure assessment. Finally, whether an additional safety factor is warranted due to residual concerns regarding the adequacy of the risk assessment (including both the hazard and exposure assessments) or regarding the degree of concern for pre- or postnatal toxicity will be considered in a weight-of-the-evidence approach during the risk characterization process. The final decision on the FQPA Safety Factor would be based on the integration of the results from each of these three steps of the risk assessment process.

The recommendation concerning the FQPA factor is made in the course of the risk assessment process as the risk characterization is being developed and the hazard and exposure assessments are being completed. The recommendation is based upon consideration of the nature

and level of confidence in the hazard and exposure assessments, the degree of concern for potential toxicity to the fetus, infants and children, and any residual uncertainties that are not accounted for in the hazard and exposure assessments. The final decision on the FQPA Factor is made, informed by the science presented in the risk characterization and the recommendation.

D. Core Elements of OPP's Policy on the FQPA Safety Factor

1. Pesticides Covered by the FQPA Safety Factor

The 1996 amendments to FFDCA state that the Agency shall assess risk to infants and children and consider the FQPA 10X Safety Factor when “establishing, modifying, leaving in effect, or revoking a tolerance or exemption for a pesticide chemical residue...” Thus, at a minimum, any pesticide with a use pattern which would require a tolerance or an exemption from a tolerance might be expected to require an FQPA Safety Factor decision. In fact, however, it is possible to make an FQPA Safety Factor decision only in those cases where the required and necessary toxicology data allow or support the derivation of a hazard value, such as an acute or chronic reference dose (RfD). Without such a hazard value, it would be inappropriate to conduct a safety factor analysis. Because of the pesticides' inherent toxicity, FQPA Safety Factor findings are generally needed for food-use pesticides of “conventional” chemistry. Examples of substances that might be excluded are the active components in plant pesticides, microbial and some other biopesticides, as well as some “inert” ingredients.

2. Population Subgroups Covered by the FQPA Safety Factor

The law states that the FQPA 10X Safety Factor shall be applied “for infants and children.” OPP, along with the rest of the Agency, in fact, is concerned about the potential for effects of concern appearing as a consequence of exposure before conception, during the prenatal stages, infancy and childhood until the time of sexual maturation. Thus, if it is anticipated that children of any age up to full sexual maturation (which in humans spans the age range from 18-21 years of age) or females of child-bearing age (characterized as “females aged 13+”) are among the exposed populations, an FQPA Safety Factor determination would be made during the risk assessment and risk management process. On rare occasions, it may also be appropriate to make an FQPA Safety Factor finding for sexually mature males, if it has been shown or would be expected that exposure to the male may lead to adverse consequences for the conceptus. If no exposure is expected for any of the aforementioned subpopulations and/or none of these subpopulations is the focus of the risk assessment being undertaken, then a determination on the FQPA Safety Factor is unnecessary, and no FQPA Safety Factor decision is incorporated into the risk assessment and risk management process.

3. New Policy Directions

a. Potential Pre- and Postnatal Toxicity

In an earlier interim policy statement describing its approach to implementation of the FQPA Safety Factor provision, OPP wrote that “reliable data support using the standard uncertainty factors (usually 100X for combined inter- and intraspecies variability) and not using the additional uncertainty factor when OPP has a complete data base and when the severity of the potential effect in infants and children, or the potency or unusual toxic properties of a compound, do not raise concerns regarding the adequacy of the traditional uncertainty factors” (OPP, 1998). Over time, OPP’s policy has continued to evolve, with greater weight being placed on the identification of increased susceptibility (either quantitative or qualitative) in the developing organism. At the present time, OPP is routinely applying an additional FQPA Safety Factor where data on a pesticide showed such increased susceptibility.

The report of the Toxicology Working Group of the Agency 10X Task Force provides a set of factors for judging the degree of concern regarding the potential of a particular pesticide to produce pre- and/or postnatal effects. OPP finds these factors useful when reaching a judgment about the importance of these data. While some of the concerns regarding pre- and postnatal toxicity may be addressed when the acute or chronic RfD is based on the pre- or postnatal endpoints in the offspring, this may not be adequate when faced with data which suggest a significant degree of concern. To the extent that these greater concerns regarding pre- and postnatal toxicity cannot be addressed through the setting of the RfD, the residual concerns or uncertainties will be addressed by the use of an additional safety factor in the final stage of the risk assessment process.

b. New Data Requirements

In this policy document, OPP, for the first time, addresses the question of how additional safety factors should be applied in situations where a toxicology database is considered incomplete given changes in data requirements. In the future, OPP may develop a similar decision logic regarding exposure data. This complex problem was not expressly addressed by Congress in the FQPA Safety Factor provision or elsewhere, leaving OPP with a fair degree of policy latitude. In devising a solution to this problem, OPP believes it is important to facilitate the development of complete data so that, as much as possible, pesticide regulation proceeds from informed scientific judgment, not default factors based on a lack of information.

V. CONSIDERATIONS RELATED TO THE UNDERSTANDING OF THE HAZARD POTENTIAL IN THE ASSESSMENT OF RISK TO INFANTS AND CHILDREN

This section will describe the issues related to the completeness of the toxicology database and the degree of concern for pre- and postnatal effects that must be considered when making an FQPA Safety Factor finding for a particular pesticide.

A. Accounting for the Completeness of the Toxicology Database and Application of the Database Uncertainty Factor

The FQPA Safety Factor is designed to account for, among other things, the “completeness of data with respect to . . . toxicity to infants and children.” This section of OPP’s policy guidance discusses how OPP will judge the completeness of the toxicology database **into** when assessing risks to children and infants and in determining whether the FQPA Safety Factor should be 10X or some different value. This section discusses OPP’s policy and practice since 1996, the recommendations of the Toxicology Working Group of the Agency 10X Task Force, and the changes that OPP is making to its policies and practices in light of those recommendations.

As explained more fully below, OPP believes that the determination of the completeness of the toxicology database for any particular pesticide must be made on a case-by-case basis, after consideration of a wide range of information. Nonetheless, OPP generally agrees with the view of the Toxicology Working Group that certain types of hazard data should be available for virtually all conventional food use pesticides (a recommendation consistent with existing OPP practices); therefore, OPP is refining the concept of a “core toxicology database.” The presence or absence of studies in the core toxicology database is the key consideration regarding application of the database uncertainty factor. OPP’s default position would generally be that if one or more of the key studies in the core toxicology database is missing or inadequate, an additional database uncertainty factor would be needed and that this database uncertainty factor should be used in derivation of the Reference Dose(s) for a chemical.

Moreover, OPP also agrees with the Toxicology Working Group that OPP should expand the scope of its data requirements for conventional food-use pesticides to include new types of studies that previously have not been routinely required, specifically the developmental neurotoxicity study, the acute neurotoxicity study in adult rats, and two immunotoxicity studies -- one in adult rats and the other in an *in vitro* system. Further, OPP agrees that these four studies should, at the appropriate time, become part of the core toxicology database.

One important issue not addressed in the Toxicology Working Group report was how OPP should implement the core toxicology base concept as regards new studies and updates or revisions to existing studies. For reasons set forth below, OPP has decided that a new study would not become part of the core toxicology database until the study has become a routine data requirement and experience has been gained in interpreting its significance and usefulness in the hazard assessment process.

For the transitional period between when a new study, or a revision to an existing core database study, is identified as a data requirement and it becomes part of the core toxicology database, any additional uncertainty/safety factor that is used to address the lack of the new or updated study will not be treated, or referred to, as a database uncertainty factor because database uncertainty factors have not been generally applied by OPP or other parts of the Agency

to address new data requirements. OPP believes that use of an uncertainty/safety factor to address new data requirements falls under that aspect of the FQPA Safety Factor that is an expansion of past OPP practice. Accordingly, OPP will analyze use of such uncertainty/safety factors both at a different stage of risk assessment than is the traditional database uncertainty factor, and in a different manner. Decisions on uncertainty/safety factors that address new requirements will not be considered during the hazard assessment but at the risk characterization stage. Further, OPP's default position when a newly identified study is lacking will not be that an additional uncertainty factor is necessarily mandated. Rather, OPP's approach will be to evaluate the existing toxicological database on a pesticide to determine if the absence of the new data is so key as to warrant an additional uncertainty factor to protect the safety of infants and children.

1. Past OPP Policy and Practice With Respect To the FQPA Safety Factor and the Completeness of the Toxicology Database

a. Hazard Identification

The starting point for any consideration of the completeness of the database for assessing the potential hazard of a pesticide to infants and children is the existing regulation requiring data to support the registration or reregistration of a pesticide used in or on food. This regulation, 40 CFR Part 158, establishes requirements for a set of toxicology data. The studies are generally grouped into either Tier 1 (i.e., studies required for all conventional food-use pesticides) or Tier 2 (i.e., studies which are “triggered” by the results of Tier 1 studies or by some special characteristic of the pesticide such as its chemical class.) 40 CFR Part 158 also contains both a waiver provision, which allows OPP to waive on a case-by-case basis an otherwise applicable requirement, and a provision that authorizes OPP to impose additional data requirements on a case-by-case basis. Together, these two provisions enable OPP to tailor the data requirements for a particular pesticide to match its specific characteristics.

The current version of 40 CFR Part 158 was promulgated in 1984; OPP's practice has evolved over the years since 1984, as the general scientific understanding of the potential hazards of pesticides has grown. Although the current practice corresponds in most respects to the existing data requirements regulation, the following description is intended to reflect OPP's recent practices.

40 CFR 158.340 (Subpart F) sets out the data requirements for “conventional chemical” food-use pesticides. For the purpose of this discussion, the current and proposed toxicology data requirements are organized into several different categories (Groups A-E), as explained below and tabulated in Table 1.

Table 1. Complete toxicology data set for a food-use pesticide

Group	Tier a	Guidelines Available	Part 158 b	Studies
A	1	Y c	Y	Acute oral toxicity Subchronic (90-day) feeding studies in rodent and nonrodent Chronic feeding studies in rodent and nonrodent Carcinogenicity studies in two rodent species Prenatal developmental toxicity studies in rodents and nonrodents Two-generation reproduction study in rodents General metabolism study in rodents Mutagenicity studies (in vivo and in vitro assay of gene mutation, structural chromosomal aberration, and other genomic effects)
B	1	Y d	Y	Acute dermal Acute inhalation Primary eye irritation Primary dermal irritation Dermal sensitization
C	2	Y	Y	Dermal penetration 21-day dermal study (rat) Subchronic (90-day) inhalation or dermal study Acute or subchronic (90-day) delayed neurotoxicity in hens Subchronic neurotoxicity studies in mammals
D	2	Y	N	Acute neurotoxicity study in mammals Immunotoxicity studies: a. Enhancement of observations in subchronic or chronic studies b. Primary antibody response to sheep red blood cells Developmental neurotoxicity in rodents Chronic neurotoxicity in mammals Scheduled controlled operant behavior Peripheral nerve function Sensory evoked potential
Ee	2	N	N	Studies designed to investigate specific concerns, for example: Pharmacokinetics in fetuses and/or young animals Direct dosing of the offspring prior to weaning Enhanced developmental neurotoxicity including specialized testing of sensory and/or cognitive function Developmental immunotoxicity Developmental carcinogenesis Enhanced evaluation of potential to induce effects related to endocrine disruption

- a Tier 1 studies are required for all food-use chemicals; Tier 2 studies are triggered by potential use and exposure patterns, chemical attributes, toxicological findings, or potential concerns identified in Tier 1 studies.
- b Cited in 40 CFR Part 158.340 Toxicology Data Requirements as described in this table.
- c Assessment of oral (dietary) exposure.
- d Assessment of non-dietary exposure.
- e The studies in this category are discussed below in connection with the recommendations of the Toxicology Working Group of the Agency 10X Task Force as future revisions/updates to current guidelines or implementation of new guidelines.

Group A consists of those studies in Tier 1 which relate to the understanding of the potential for hazard attendant to oral (i.e., dietary) exposure and currently include:

1. An acute oral toxicity study
2. Two subchronic (90-day) feeding studies (one each in a rodent and nonrodent)
3. Two chronic feeding studies (one each in a rodent and nonrodent)
4. Carcinogenicity studies in each of two species of rodents
5. Two prenatal developmental toxicity studies in rodents and nonrodents
6. A two-generation reproduction study in rodents
7. A general metabolism study in rodents
8. Mutagenicity studies (*in vivo* and *in vitro* assays of gene mutation, structural chromosomal aberration and other genomic effects)

Group B consists of the existing data requirements in Tier 1 for “conventional chemistry” food-use active ingredients that provide understanding of the hazard and risk potential from non-dietary routes of exposure of a food-use pesticide (e.g., for professional mixers/ loaders/ applicators, the general population using a home-use product or anyone who may be exposed after application in the fields or around the home or public places such as schools or parks). Group B includes:

Five acute toxicity studies (acute dermal, acute inhalation, primary eye irritation, primary dermal irritation, and dermal sensitization)

Depending upon potential use and exposure patterns, chemical attributes, or findings in the required studies, specialized studies may be conditionally required for any chemical or chemical class. Conditionally required (Tier 2) studies, for which testing guidelines currently exist, include those listed below (Group C):

1. Dermal penetration study
2. 21-Day dermal study
3. Acute or subchronic (90-day) delayed neurotoxicity studies in hens
4. Subchronic neurotoxicity studies in mammals
5. Subchronic (90-day) inhalation or dermal study

Finally, there are several toxicity studies for which guidelines exist but which are not currently listed in Part 158 (Group D). These Group D studies can be imposed on a case-by-case basis. They include:

1. Acute neurotoxicity studies in mammals
2. Two immunotoxicity studies (one is an enhancement of observations in the 90-day and/or chronic repeated dose studies, the other measures a primary antibody response to sheep red blood cells)
3. Developmental neurotoxicity study in rodents

4. Chronic neurotoxicity study in mammals
5. Scheduled controlled operant behavior
6. Peripheral nerve function
7. Sensory evoked potential

The Group D studies include the developmental neurotoxicity study, which has been the focus of a great deal of attention since FQPA was passed. Developmental neurotoxicity testing can provide data that are useful in characterizing hazard and dose response in young animals exposed prenatally through weaning. Up until the present time, the need for developmental neurotoxicity studies has been identified on a case-by-case basis. OPP's determination has been based upon a weight-of-the-evidence evaluation of the available toxicology data along with particular consideration of five criteria or "triggers" from data such as those on adults (e.g., the Group C and D acute and/or repeated dose neurotoxicity studies in adult animals) and/or the Group A prenatal developmental toxicity and multigeneration reproductive toxicity studies. These criteria, along with several other factors, are considered in a weight-of-the-evidence review of all available data for each chemical.⁴ The criteria require that the substance has been shown to:

- 1) cause central nervous system (CNS) malformations following prenatal exposure;
- 2) affect brain weight in offspring, which does not appear to be related solely to general growth retardation, following pre- and/or postnatal exposure.
- 3) cause neuropathology in developing or adult animals or neuropathy in humans;
- 4) cause persistent functional changes in the offspring which may be the result of effects on the nervous system;
- 5) act to significantly alter hormonal responses associated with the development of the nervous system, leading to significant development effects (e.g., effects on sexual maturation).

b. The Use of Uncertainty Factors in Dose Response Assessments

Once OPP has assembled the toxicology database on a particular pesticide, it reviews these data to analyze the relationship between dose and response, that is, the levels at which the pesticide causes adverse effects in test animals. Dose response assessment of the potential for

⁴Based upon SAP review of the five criteria listed above and upon subsequent Panel recommendations, OPP has proposed two additional criteria that would be used to trigger the developmental neurotoxicity study. These criteria specify that the study would be required for any chemical which has been shown to:

- 1) act as a neurotoxicant in insects, unless other information about the chemical, such as pharmacokinetic or pharmacodynamic data, demonstrate the inappropriateness of such testing; or
- 2) cause evidence of adverse effects in tests of cognition, memory, and other higher brain functions.

adverse health effects of pesticides occurring in infants and children is part of the overall dose response assessment for health effects in general. That is, the data on developmental toxicity are evaluated along with the data on adults and the NOAEL or BMD for the most sensitive or critical effects is based on consideration of all health effects. By doing this, protection of children's health will be considered along with that of other sensitive populations. In some cases, it is appropriate to evaluate the potential hazard to children separately from the assessment for the general population or other population subgroups.

The dose response assessment for pre- and postnatal toxicity involves defining an appropriate no-observed-adverse-effect level (NOAEL), or a lowest-observed-adverse-effect level (LOAEL), if a NOAEL is not available. The dose response data also may be fit using a modeling approach and an effective dose (ED) estimated for a given level of response. For example, the ED₀₅ is an effective dose that produces a 5% response level above background. A lower confidence limit on the ED (i.e., the LED) may be used as a benchmark dose (BMD). There are several levels of response that may be used to calculate the BMD, e.g., 10%, 5%, 1%. (BMD₁₀, BMD₀₅, BMD₀₁). There is ongoing discussion in the Agency about the appropriate level to use for extrapolation to lower dose levels when deriving an RfD.

The NOAEL or BMD, whichever is used as the point of departure, can be used in two ways in risk assessment: First, it can be divided by uncertainty factors to account for various uncertainties in the data (see below) and this value used to set the RfD. Second, the NOAEL or BMD can be divided by the human exposure estimate (actual or projected as a goal) to derive a margin of exposure (MOE) that can be used to determine whether existing or proposed controls on exposure of humans meet the "reasonable certainty of no harm" standard.

For over fifteen years, EPA has been deriving chronic RfDs, using a consensus approach developed by the Agency's first RfD Workgroup. The Agency's original approach is described in, for example, Dourson and Stara (1983), Barnes and Dourson (1988) and other publications and in a separate file on the Agency's Integrated Risk Information System (IRIS) database website (EPA, 1997). While some minor changes may have occurred over the years as the Workgroup developed chronic RfDs for use by the Agency as a whole, no formal reconsideration of the basic elements of that approach has been undertaken. OPP follows the Agency's consensus approach.

Five uncertainty factors and one modifying factor have been identified for application to the NOAEL or BMD to derive hazard values such as the acute or chronic reference dose (RfD). These include the following: 1) the interspecies uncertainty factor which is intended to account for the uncertainty involved in extrapolating from animal data to humans; 2) the intraspecies uncertainty factor which is intended to account for the variation in sensitivity among the members of the human population including children; 3) an uncertainty factor to extrapolate from subchronic to chronic data, if deriving a chronic RfD; 4) an uncertainty factor to extrapolate from the LOAEL to the NOAEL, if no appropriate NOAEL can be identified in the toxicology database, and 5) an uncertainty factor to account for the absence of key data sets in the database for a given chemical. An additional modifying factor may also be applied when scientific

uncertainties in the study chosen for derivation of the RfD exist or when other aspects of the database are not explicitly addressed by one or more of the five uncertainty factors (e.g., statistically minimal group sample size or poor exposure characterization). The maximum default value for each of the five uncertainty factors and the modifying factor is 10, although sometimes a different factor (often 3X) is used, depending on the nature and quality of the information available on the pesticide. The composite uncertainty/modifying factor is never to exceed 10,000, and, in practice, rarely exceeds 1000, particularly for pesticides.

The **intraspecies uncertainty factor** and the database uncertainty factor are especially relevant to protecting children's health, in the context of implementation of FQPA and the application of the FQPA Safety Factor. The intraspecies uncertainty factor is applied to account for variations in susceptibility within the human population (including children). Various authors have evaluated the intraspecies uncertainty factor using data from animal or human studies, as summarized by Dourson et al. (1996). (Further discussion of this literature can be found in the report of the Toxicology Working Group.)

The **database uncertainty factor** is applied when the available toxicological database is lacking in one or more of the studies deemed necessary in order to derive an RfD of "high confidence." When the Agency's RfD approach was originally developed, the minimum database of animal studies necessary for a "high confidence" (chronic) RfD consisted of a) two chronic studies in different species; b) two prenatal developmental toxicity studies in different species, and c) a two-generation reproduction study. An RfD is believed to provide an estimate of daily exposure over a lifetime presenting no appreciable risk to all segments of the population, including children. In light of the fact that all five of these studies are required in the first tier of testing for a food-use pesticide, it is rarely necessary to apply or retain a database uncertainty factor greater than 1X for a pesticide once its registration and first food use are approved.

While the database uncertainty factor has not been used in OPP to account for the lack of a developmental neurotoxicity study, OPP has taken the need for this study into account in making its FQPA Safety Factor decisions. When the need for the developmental neurotoxicity study has been triggered, the uncertainty or concern which exists until the study results are available and evaluated is accommodated in the FQPA Safety Factor decision.

2. The Recommendations of the Toxicology Working Group of the Agency 10X Task Force

The report of the Toxicology Working Group of the Agency's 10X Task Force contains several recommendations that, if implemented, would result in changes to OPP's policies and practices in the implementation of the FQPA Safety Factor provision. First, the Working Group redefined the concept of a "core toxicology data base," which describes the types of data that would be needed to evaluate the potential hazards to infants and children for virtually all conventional food-use pesticides. Second, the Working Group recommended that OPP include in the core toxicology database a number of studies that OPP has not routinely required. Third, the

Working Group recommended that, whenever the core toxicology database was not complete, OPP should impose an additional factor, the “database uncertainty factor,” to account for the possibility that a particular pesticide might be more toxic to infants or children than is indicated by the available data. Finally, the Working Group concluded that, if imposition of an additional database uncertainty factor fully accounted for missing data, the completeness of the toxicology database then was not a basis for imposing the default 10X FQPA Safety Factor.

a. Data requirements

The Working Group recommended that OPP employ the redefined concept of a “core toxicology database” in evaluating whether the Agency possesses complete data to evaluate the potential hazard of a pesticide to infants and children. Typically, in the evaluation of hazard and dose response, a broad selection of toxicology studies is used to evaluate each chemical. The types of studies included in a core data set are intended to characterize hazard after exposure for varying lengths of time (a single exposure, exposure over several days or weeks, and chronic or lifetime exposure), and by different routes of exposure (oral, dermal and inhalation), depending on the route(s) of concern and the exposure scenarios identified for incorporation into an aggregate risk assessment. In addition, the core studies attempt to screen for toxicity to various organ systems in adult and developing animals. More specific testing of organ system function is included for some endpoints (e.g., reproductive toxicity, neurotoxicity, immunotoxicity) that would not be adequately assessed in the toxicity studies included in the original core data set.

The Working Group recommended that the core toxicology database include these: all Group A studies; Group B studies if humans would also be exposed to the food-use pesticide by other pathways, e.g. dermally or by inhalation; and Group C studies, if triggered, except for the subchronic neurotoxicity study in mammals which should become a Tier 1 (i.e., Group A) study. The Working Group also recommended that the types of studies required on a routine basis be expanded beyond those that OPP had previously included. Specifically, the Working Group recommended that OPP routinely require the acute and subchronic neurotoxicity studies in mammals, both immunotoxicity studies, and the developmental neurotoxicity study in Tier 1 for all food-use pesticides and the remaining Group D studies, if triggered, and include them in the core toxicology database. The Working Group also recommended a number of guidelines be developed for additional studies, many of which could be conducted by making modifications to the testing methodology for currently required studies. These “Group E” studies are discussed below.

The Working Group believed that the criteria/triggers used by OPP to decide whether a developmental neurotoxicity study should be required were probably a reasonable place to start. The criteria, however, were based on experience with a very limited number of agents, and more recent information suggests that these triggers may not be inclusive enough to identify and subject to testing all chemicals that have the potential to produce developmental neurotoxicity. Based on the data currently available, the Working Group concluded that it is not possible to predict how many neurotoxic agents will demonstrate developmental neurotoxicity, nor is there currently

sufficient information to predict how many agents that are not neurotoxic in adult animals or that do not cause central nervous system malformations will cause developmental neurotoxicity (for further discussion, see the Working Group's report). Therefore, the Working Group recommended that the developmental neurotoxicity study become a Tier 1 data requirement for all conventional food-use pesticides.

In addition, as mentioned above, the Working Group recommended that existing guidelines for conducting certain types of studies be modified/updated or new guidelines created for studies which would expand OPP's capacity to understand the potential for pre- and postnatal toxicity to infants and children. These studies would be conducted and considered part of the core database for a specific chemical, on a case-by-case basis, if the results of Tier 1 studies indicate the potential for concern for infants and children.

These (Group E) include:

1. Expansion of the metabolism/pharmacokinetic guidelines to include evaluation of the fetus during prenatal exposure and the neonate/very young organism postnatally.
2. Development of guidelines for when and how direct dosing of offspring (oral, inhalation, or dermal) prior to weaning should be done. This would be applicable for a number of different studies.
3. Enhanced developmental neurotoxicity studies which include specialized testing of sensory and/or cognitive function.
4. A developmental immunotoxicity study.
5. A developmental carcinogenesis study (i.e., inclusion of an *in utero* and/or perinatal exposure segment in the cancer bioassay).
6. Enhanced evaluation of the potential to induce effects related to endocrine disruption (e.g., further upgrading of the multigeneration reproduction study and/or the assays in the screening battery of EPA's proposed Endocrine Disruptor Screening Program).

b. The Use of Uncertainty Factors in Dose Response Assessments

Once the scope of the core toxicology database has been defined for a particular pesticide, the Working Group recommended that, whenever the core toxicology database (with the broader scope recommended above) was not complete, OPP should impose a "database uncertainty factor" to account for the possibility that a particular pesticide might be more toxic to infants or children than is indicated by the available data. The size of the database uncertainty factor applied will depend on other information available in the database and how much impact the missing data may have on determining the potential hazard of the pesticide for children. The Working Group further indicated that, if a database uncertainty factor had been employed in deriving the RfD that was considered to have adequately accounted for the lack of certain toxicity data, the completeness of the toxicology database was not then a basis for imposing the default 10X FQPA

Safety Factor.

The default value of 10X for the intraspecies uncertainty factor is considered adequate in the majority of cases for protecting children's health, when a complete core toxicology database is available. The Working Group underscored that reduction of the 10-fold intraspecies uncertainty factor should occur only in those cases where the data are complete and the age group or window of vulnerability during development has been clearly delineated, and the relevance of animal data to humans is clearly understood. Rarely can the intraspecies uncertainty factor be reduced to 1X and only if variability in children at various ages due to genetic, lifestyle, and other influences can be shown not to be a factor.

3. The OPP Policy With Respect to the Completeness of the Toxicology Database, the Database Uncertainty Factor, and the FQPA Safety Factor

The determination regarding the completeness⁵ of the toxicology database for a food-use pesticide, in the context of aggregate risk assessment, is one of the three primary considerations relative to the FQPA Safety Factor. After reviewing the report of the Toxicology Working Group of the Agency 10X Task Force, OPP has determined that its past policy and practice are largely consistent with the Working Group's framework and recommendations. Therefore, OPP will continue, and build upon, the basic approach described above. Central to that approach is the principle that an analysis must be performed for each pesticide, using a weight-of-the-evidence approach, in order to arrive at a conclusion regarding the completeness of the toxicology database for that pesticide. The completeness of the data set is defined by many factors that include, but are not limited to, the availability of a core set of toxicology studies, with any necessary conditionally-required or supporting data, that allow scientists to arrive at a supportable conclusion regarding the toxicological potential of the chemical to adversely affect infants and children and the degree of concern those findings raise.

a. Data Requirements

OPP has decided to make several changes in its approach to the assessment of the completeness of the toxicology database. First, OPP is adopting the Toxicology Working Group's recommendation to employ the concept of a core toxicology data set in its approach to evaluating the completeness of the toxicology database. In addition, OPP agrees that it is

⁵Hazard data must also be reliable. The reliability of the data set is based in part on the Agency's testing guidelines which are implemented using Good Laboratory Practices and which have been designed to provide reliable data on the hazard potential of agents. Reliability is also evaluated through use of scientific judgment considering factors such as the quality of the testing and reporting, the concordance of findings among studies (including those conducted according to Agency guidelines as well as those found in the open literature), and the overall confidence in the available data.

appropriate to identify the studies which should be considered to be part of the core data set.

To that end, OPP has developed criteria for judging whether a particular study should be in the core toxicology data set for a conventional food use pesticide. In sum, these criteria describe a core toxicology data set as consisting of those types of routinely required studies, which experience has shown are capable of evaluating an aspect of the hazard of a pesticide which is not adequately assessed by other types of studies. As discussed below, application of these criteria leads OPP to expand immediately the scope of the core database it has historically considered. Moreover, the Toxicology Working Group's evaluation of the state of the science leads OPP to take additional steps that should result in even greater expansion of the core toxicology database in the future, although not to the extent, or at the pace, the Toxicology Working Group recommended.

OPP will use the following criteria to judge whether a specific type of study should be part of the core toxicology data set:

- 1) whether there are peer-reviewed, publicly available guidelines for the conduct of the study or standard, well-documented protocols for use in conducting such studies; and there is consensus in the scientific community that it is worth the effort to conduct such a study on a regular basis because it would produce data valuable to the understanding of the potential hazards to humans, including infants and children;
- 2) whether the data from this type of study are routinely required (i.e., required either as part of OPP's data requirements rule or under a well-established policy and practice for registration and reregistration/renewal), and whether the requirement has resulted in the generation and submission of the data with which the Agency has acquired experience in evaluating;
and
- 3) whether there is consensus in the scientific community that there is now a body of evidence supporting the conclusion that it was worth the effort to conduct such an effort because the results of this type of study do improve, in a significant way, the understanding of the potential hazard of the pesticide to infants and children.

In general, when data from key studies which are considered part of the core toxicology database are not available, OPP would likely impose a database uncertainty factor in deriving the RfD. It should be noted that the absence of a study that is not, or not yet, part of the core database could also lead to the use of an additional safety factor; that is, OPP will still consider the absence of the non-core study for a particular pesticide in making its FQPA Safety Factor decisions. Therefore, this approach to determining whether a particular type of study has become part of the core toxicology database, and warrants routine application of a database uncertainty factor, does not end OPP's analysis of the impact of the completeness of the toxicology database or the need for an FQPA Safety Factor. Rather, in individual cases, OPP may determine that the missing data (while not part of the "core toxicology database") are nonetheless important to the understanding of the potential hazards to infants and children of the pesticide and, therefore, that an FQPA Safety Factor is appropriate.

For a study to be included in the core toxicology database, OPP, or some other regulatory or international scientific organization, should first have issued guidelines describing how to perform the study. Also, there may be standard, well-documented testing protocols available in the scientific community that can be easily referenced. OPP does not think that it is appropriate to consider a study as part of the core set of toxicology studies expected to be available to assess the risks to infants and children if there are no written descriptions of the test methodology available for performing such a study.

Second, to be included in the core set of toxicology studies for pesticides, data from the tests must be routinely required under FIFRA and FFDCA, as evidenced either by a data requirement (Tier 1 or Tier 2) in OPP's data requirements regulation, 40 CFR Part 158, or by a well-established policy and practice of requiring the data both for registration and reregistration/renewal of similar pesticides. The existence of a data requirement in Part 158 or a well-established policy and practice communicates to the regulated community, the scientific community and other stakeholders what OPP's expectations are regarding the need for toxicology data to assess the risks of a pesticide to infants and children. Moreover, OPP must have allowed sufficient time for those test sponsors subject to the requirement to conduct the tests and submit the results to OPP. With notice and adequate time, it is appropriate to expect that such data will routinely be available for review in evaluating the potential hazards from exposure of infants and children to a pesticide. Conversely, if OPP has not taken steps to impose a data requirement or has not allowed sufficient time for the studies to be performed, it is not realistic to expect that the data be considered part of the core toxicology data set.

Third, OPP will include a specific type of study in its core toxicology database when there is a body of evidence supporting the conclusion that the results establish that this particular kind of study contributes in a significant way to the overall understanding of the potential hazard of pesticides to humans, including infants and children. Scientifically, the understanding of the hazard potential of substances grows with the availability and analysis of more information. Initially, there is often great controversy within the scientific community about whether a chemical can cause a particular type of adverse effect. Usually, after sufficient data are presented and peer reviewed, consensus emerges that at least some individual substances do, or do not, cause an specific type of adverse effect, and, therefore, it may be prudent to require studies to be performed on other, similar, untested chemicals. The determination that further routine testing is warranted does not mean, however, that all tested substances will cause the particular adverse effect or that they will do so at a dose level which is lower than any other previously identified adverse effect. Understanding of the likely significance of a new study is often apparent only after the scientific community has had considerable experience reviewing data from the test method on a variety of substances from different chemical classes. This kind of experience, gained from the review of studies by OPP or others, is the last ingredient necessary for OPP to determine whether a particular study is likely to identify new effects or effects at lower levels that could significantly change the outcome of its overall risk assessment, or alter, in other ways, the registration status of a chemical. Once the database supports such a conclusion -- as it does for the Group A, B, and

(when triggered) Group C studies -- OPP will establish, as a broad policy, that the absence of that particular sort of study warrants routine application of a database uncertainty factor.

OPP has applied the three criteria and determined that, for the purpose of evaluating the completeness of the toxicology database, the core toxicology data set generally will consist of:

- a) those Part 158 Tier 1 studies currently required to evaluate exposure by the oral route(s)/pathway(s) of concern (i.e., Group A);
- b) those Part 158 Tier 1 studies currently required to evaluate exposure by other route(s)/pathway(s) of concern (i.e., Group B, if non-food use exposure sources are expected);
- and
- c) any Group C Part 158 Tier 2 conditionally required studies triggered by the results of the Tier 1 studies or by chemical class characteristics (e.g., the delayed neurotoxicity study in hens for cholinesterase-inhibiting organophosphate insecticides).

Group C includes the subchronic adult neurotoxicity study, which currently is conditionally required when acute studies on a pesticide show neuropathy or neurotoxicity. OPP has already received and reviewed the results of the subchronic neurotoxicity study in adult rats, as well as the acute neurotoxicity study in adult rats, for over 60 pesticides. Based on its experience with these results, and on the recommendation of the Toxicology Working Group of the Agency 10X Task Force, OPP has decided to propose that it will routinely impose a requirement for both the acute and subchronic neurotoxicity studies in adult rats on all conventional food-use pesticides (i.e., confer Group A status on them). The acute and subchronic neurotoxicity studies in adult rats, in addition to allowing evaluation of the potential for neurotoxicity, in general, also provide a basis for comparison of the potential for age-related differences in impacts on the nervous system with results from the developmental neurotoxicity study on the same chemical, when available. Since OPP has already concluded that the two neurotoxicity studies in adult animals meet the first and third criteria, these data requirements will become part of the core toxicology database, once they are routinely required and OPP has allowed adequate time for the generation and submission of these data.

At the present time, the studies in Group D do not meet either the second or the third criterion, and, therefore, none is a part of OPP's current core toxicology database. However, based on the recommendation of the Toxicology Working Group, OPP intends to make the Group D studies routine Tier 1 or Tier 2 requirements, by including these studies in its proposed revisions to 40 CFR Part 158, to be published this year. The acute neurotoxicity study in adult rats, the two immunotoxicity studies, and the developmental neurotoxicity study are likely to be proposed as Tier 1 requirements, the others as Tier 2 requirements. OPP believes that the Working Group report presents a strong argument that the developmental neurotoxicity study, in particular, is capable of identifying adverse effects not evaluated in other test systems and that the data might lead to a lower NOAELs and RfDs. In addition, OPP has decided to begin the process now of issuing data call-in notices under the authority of FIFRA section 3(c)(2)(B) to require

submission of the developmental neurotoxicity study (along with the acute and subchronic neurotoxicity studies in adult rats) for certain currently registered food use pesticides⁶. As noted earlier, two additional criteria have been proposed to be used in addition to the original five criteria that have been used to trigger the developmental neurotoxicity study. All seven criteria will be applied by OPP as factors in the decision logic for requesting the conduct of this study in the data call-in notice. These criteria are applied in the context of a weight-of-the-evidence assessment of the entire existing toxicology database, at which time all information pertinent to the assessment of the hazard potential (including neurotoxicity) of the chemical is considered, along with any other information which may indicate special sensitivity to the young or other age-related differences.

As discussed elsewhere in this document, it is understood that there may be a need to develop additional specialized test guidelines that address specific target organs and endpoints. However, until these new guidelines are developed and the need to conduct them on a routine or a conditional basis (based on triggers from other studies) is assessed, these additional studies (Group E) will not be included in the core database at this time. In cases where concerns are raised about the possibility of other pre- and/or postnatal effects that are not assessed in the core database, OPP may ask for chemical-specific special (i.e., non-guideline) studies evaluating the health effects of concern. These studies also will not be considered part of the core database until such time as their study design has been agreed upon, and the data generated, submitted and reviewed by OPP.

When OPP makes its intended changes to the data requirements in Part 158, the categorization of studies into Groups A, B, C and D will have changed. Group D will become a null set. The new categorization is shown in Table 2, below:

⁶ At its March, 1998, the FIFRA Scientific Advisory Panel recommended that the developmental neurotoxicity study be conducted for any pesticide that works by poisoning the nervous system of insects. The early data-call-in process will include those food-use chemicals that meet this criterion. The Panel did not reach consensus on whether or not the developmental neurotoxicity study should be required for all pesticides. As noted above, OPP plans to include this study as a Tier 1 requirement for all conventional food-use pesticides, as recommended by the Toxicology Working Group, when it proposes revisions to Part 158 later this year.

Table 2. Complete toxicology data set for a food-use pesticide following intended revisions to Part 158

Group	Tier a	Guidelines Available	Part 158 b	Studies
A	1	Y c	Y	Acute oral toxicity <i>Acute neurotoxicity studies in mammals</i> Subchronic (90-day) feeding studies in rodent and nonrodent <i>Subchronic neurotoxicity studies in mammals</i> <i>Immunotoxicity studies:</i> <i>a. Enhancement of observations in subchronic or chronic studies</i> <i>b. Primary antibody response to sheep red blood cells</i> Chronic feeding studies in rodent and nonrodent Carcinogenicity studies in two rodent species Prenatal developmental toxicity studies in rodents and nonrodents <i>Developmental neurotoxicity in rodents</i> Two-generation reproduction study in rodents General metabolism study in rodents Mutagenicity studies (in vivo and in vitro assay of gene mutation, structural chromosomal aberration, and other genomic effects)
B	1	Y d	Y	Acute dermal Acute inhalation Primary eye irritation Primary dermal irritation Dermal sensitization <i>21-day dermal study</i>
C	2	Y	Y	Dermal penetration Subchronic (90-day) inhalation or dermal study Acute or subchronic (90-day) delayed neurotoxicity in hens Chronic neurotoxicity in mammals Scheduled controlled operant behavior Peripheral nerve function Sensory evoked potential
D	2	Y	N	<i>None</i>
Ee	2	N	N	Studies designed to investigate specific concerns, for example: Pharmacokinetics in fetuses and/or young animals Direct dosing of the offspring prior to weaning Enhanced developmental neurotoxicity including specialized testing of sensory and/or cognitive function Developmental immunotoxicity Developmental carcinogenesis Enhanced evaluation of potential to induce effects related to endocrine disruption

- a Tier 1 studies are required for all food-use chemicals; Tier 2 studies are triggered by potential use and exposure patterns, chemical attributes, toxicological findings, or potential concerns identified in Tier 1 studies.
- b Cited in Part 158 Toxicology Data Requirements as described in this table.
- c Assessment of oral (dietary) exposure.
- d Assessment of non-dietary exposure.
- e The studies in this category are discussed in connection with the recommendations of the Toxicology Workgroup of the Agency 10X Task Force as future revisions/updates to current guidelines or implementation of new guidelines.

b. The Use of Uncertainty Factors in Dose Response Assessments

The availability of a core toxicology data set is closely related to the assessment of the potential of a pesticide to cause prenatal or postnatal toxicity and the decision regarding the need for a database uncertainty factor. The purpose of including in this policy a description of the types of studies that, in general, are needed in the core toxicology data set, is to establish a set of clear expectations, with regard to conventional food-use pesticides, of the types of data that would best allow the assessment of potential hazards to infants and children. While every study may contribute some information that may be valuable to this assessment, not every study carries the same weight in providing that information, either for hazard identification or dose response assessment. The question of how adequately the available database addresses all of the hazards that a pesticide may present is appropriately dealt with in making a decision regarding whether an additional database uncertainty factor and/or some factor in addition to the database uncertainty factor is needed.

OPP will determine the need for a database uncertainty factor, based upon the presence or absence of one or more of the studies originally identified by the Agency as necessary for a “high confidence” (chronic) RfD: the two chronic studies in different species, the two prenatal developmental studies in different species and the multigeneration reproductive toxicity study. In addition, OPP will extend this practice to the subchronic adult neurotoxicity study, if it has been triggered, but the data have not yet been submitted, reviewed and deemed acceptable. In other words, the absence of one or more of these six studies will prompt the application of a database uncertainty factor of greater than 1X. The size of the database uncertainty factor will depend upon how many and which studies are missing. OPP intends to continue to follow the traditional Agency practice of using a 3X if one study is missing, and the full 10X if more than one is missing.

Where OPP lacks data from other studies (other than the six mentioned above), including data from studies which are newly required and not yet part of the core toxicology database, the significance of their absence will be considered in the FQPA Safety Factor decision. The specific implications of the absence of the new data requirements set forth above are discussed in section 3.c.

Once the hazard identification and dose response assessment are completed, the hazard assessment process as a whole can be characterized relative to how well it accounts for the uncertainties in the database and the degree of concern about the potential hazard of a pesticide for infants and children. This is especially important in evaluating the conservative nature of the process and if there are any **residual uncertainties** left that should be accounted for in risk characterization and/or risk management.

For the most part, the RfD process takes into account deficiencies in the toxicology database and the potential for hazard of a pesticide to infants and children. If, for some reason, an assessment which includes the derivation of hazard values such as the RfD does not meet this

standard, then the assessment would be considered to contain residual uncertainties. In these cases, one would accommodate for the remaining uncertainties by considering the use of an additional safety factor (i.e., an FQPA Safety Factor) in the final stage of the risk assessment and risk management process.

c. Evaluation of the FQPA Safety Factor for Certain Newly Required Studies Prior to Their Inclusion in the Core Toxicology Database

As set forth above, studies newly required for broad categories of pesticides generally do not become part of the core toxicology database immediately upon imposition of the data requirements. Therefore, OPP does not immediately begin to impose the database uncertainty factor in their absence. In this policy, OPP announces its intention to begin the process of requiring several studies in two stages – through data call-ins for a significant subset of conventional food-use pesticides and through revisions to 40 CFR Part 158 for all such pesticides. These particular studies have been identified as especially useful and relevant to the consideration of the potential hazard to infants and children, and OPP has somewhat limited experience with receipt and review of these studies.

Once OPP has followed through on the intention stated here and imposed requirements for these particular studies, OPP must also establish its science policy approach to how it will consider the absence of these studies as part of the FQPA Safety Factor evaluation. OPP believes that this is a critical issue of science policy and intends to develop its approach in this area through a thorough and open process involving stakeholders and the general public. As recommended by the Tolerance Reassessment Advisory Committee, OPP will issue a Notice in the Federal Register inviting public comment on its Policy Guidance for implementing the FQPA Safety Factor.

Specifically, OPP will solicit public comment on: whether and how a weight-of-the-evidence approach could be applied in circumstances where significant new data requirements have been imposed but the new data have not yet been received and analyzed; whether the absence of one or more of the specific studies contemplated for these new requirements should lead to the routine or likely retention of some or all of the FQPA Safety Factor prior to the inclusion of these studies in the core toxicology database; and whether and how OPP can identify reliable data that support removal of some or all of the FQPA Safety Factor prior to the receipt and review of these newly required studies.

OPP's approach to defining its core toxicology database and making decisions with respect to the FQPA Safety Factor is summarized in Table 3 below. The table addresses three different time frames: 1) OPP's historical practice; 2) the policy and practice described in this guidance document to be followed until the data requirements rule (Part 158) is amended; and 3) the policy and practice anticipated at such time as the intended changes to the data requirements rule are implemented.

Table 3: Transition Policies For Addressing the FQPA Safety Factor Under Developing Data Requirements for Toxicology Studies

	Historical OPP Approach	Current Policy	Policy Following Intended Revisions to Part 158
Studies expected in core toxicology database	Studies in original Groups A, B, and C (when triggered) – See Table 1	Studies in original Groups A, B, and C (when triggered) – See Table 1	Studies in expanded Groups A, B, and C (when triggered) – See Table 2
Subchronic Neurotoxicity Study	Group C, imposed on a case-by-case basis	Group C, imposed through DCIs for subject active ingredients	Group A – See Table 2
Developmental Neurotoxicity Study and Acute Neurotoxicity	Group D, imposed on a case-by-case basis when triggered by 5 criteria	Group D, imposed through DCIs for subject active ingredients when triggered by 7 criteria	Group A – See Table 2
Immunotoxicity Studies	Group D	Group D	Group A
Database Uncertainty Factor Decision	Decision about the need for and size of database uncertainty factor made on a case-by-case basis, with an uncertainty factor greater than 1X generally applied when any of the following 5 studies are absent: 2 chronic studies in different species; 2 prenatal developmental studies in different species; and a multi-generation reproductive toxicity study	Decision about the need for and size of database uncertainty factor made on a case-by-case basis, with an uncertainty factor greater than 1X generally applied when any of the following 6 studies are absent: 2 chronic studies in different species; 2 prenatal developmental studies in different species; a multi-generation reproductive toxicity study; and a subchronic neurotoxicity study	Decision about the need for and size of database uncertainty factor made on a case-by-case basis, with an uncertainty factor greater than 1X generally applied when any of the following 8 studies are absent: 2 chronic studies in different species; 2 prenatal developmental studies in different species; a multi-generation reproductive toxicity study; an acute neurotoxicity study; a subchronic neurotoxicity study; and a developmental neurotoxicity study

FQPA Safety Factor Decision	Decision about the need for and size of FQPA Safety Factor made, taking into account residual uncertainty due to gaps in the toxicology database deemed necessary for the particular chemical under consideration	Decision about the need for and size of FQPA Safety Factor made, taking into account residual uncertainty due to gaps in the toxicology database deemed necessary for the particular chemical under consideration	Decision about the need for and size of FQPA Safety Factor made, taking into account residual uncertainty due to gaps in the toxicology database deemed necessary for the particular chemical under consideration
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B. Determination of the degree of concern for potential pre- and postnatal effects on infants and children

The FQPA Safety Factor is designed to account for, among other things, “potential pre- and postnatal toxicity” This section of OPP’s policy guidance discusses how OPP will take the potential for pre- and postnatal toxicity into account when assessing risks to infants and children and in determining whether the FQPA Safety Factor should be 10X or some different value. This section discusses briefly OPP’s policy and practices since 1996, then the recommendations of the Toxicology Working Group of the Agency 10X Task Force, and concludes with the changes that OPP is making to its policies and practices in light of those recommendations.

As explained more fully below, OPP has decided to expand its historical approach to consider all of the specific factors identified by the Toxicology Working Group as indicating a higher or lower level of concern for pre- and postnatal toxicity, in particular the slope of the dose response curve. Contrary to the Working Group’s recommendation, however, OPP has decided, as a policy matter, that it will continue generally to apply an additional safety factor greater than 1X for a pesticide when data indicate infants and children appear to be more sensitive to the adverse effects of the pesticide than adults, when there is a high degree on concern. Finally, although the Working Group recommended that the consideration of the potential for pre- and postnatal toxicity should occur entirely in connection with the determination of the RfD for a pesticide, OPP has decided to continue its practice of also considering these factors at the stage of its decision-making that addresses the FQPA Safety Factor.

1. Past OPP Policy and Practice with Respect to the FQPA Safety Factor and the Potential for Pre- and Postnatal Toxicity

Since enactment of FQPA, OPP has taken different approaches to the language concerning the potential for pre- and postnatal toxicity in FQPA. Immediately after enactment of FQPA and continuing until late 1997, OPP did not impose any additional safety factor, either under FQPA or otherwise in its risk assessments, solely because children seemed to be more sensitive to the toxic effects of a pesticide than adults.

Beginning with decisions made in January, 1998, and continuing to the present, however, OPP has taken a different approach. When the available data have indicated that infants or children, because of their greater sensitivity, would experience the adverse effects from exposure to a pesticide before other age groups in the population, OPP generally has imposed an FQPA Safety Factor greater than 1X. This approach has been based on policy considerations – that OPP wants a greater level of certainty that children and infants will be adequately protected when they appear to be the most sensitive age group.

2. The Recommendations of the Toxicology Working Group of the Agency 10X Task Force

The Toxicology Working Group of the Agency 10X Task Force has recommended a weight-of-the-evidence approach for making judgments about the degree of concern for potential pre- and postnatal toxicity in humans. Several factors are included which fall into four categories of information: 1) human data on pre- and postnatal toxicity; 2) pre- and postnatal toxicity in animal studies, including whether the effects observed in young animals are of a different or similar type as those observed in adults; 3) the dose response nature of the experimental animal data, including the dose-related incidence of response, relative potency of response, slope of the dose response curve, and how well the no-observed-adverse-effect level (NOAEL) or benchmark dose (BMD) is defined; and 4) relevance of the experimental animal data to humans, including toxicokinetics, similarity of the biological response in more than one species, and knowledge of the mechanism of action. For each of these areas, factors are given for estimating a degree of concern (as high, moderate or low) for the potential for adverse effects on children's health.

The framework/approach that will be used to make judgments about the degree of concern is shown in Table 4.

Table 4. Criteria to be considered in estimating a degree of concern for children's health risks

Issue	Criteria	Degree of Concern		
		Higher	Moderate	Lower
Human data on pre- and postnatal toxicity	Sufficient data to judge effect or no effect ⁷	Effects related to exposure		No effects related to exposure
Pre- and postnatal toxicity in animal studies ⁶	Effects of a different type with different consequences in young and adults	Effects at lower dose levels than in adults	Effects at similar dose levels as in adults	No effects or effects at higher doses, minor effects (e.g., judged to be normal variations), or effects secondary to generalized toxicity
	Effects of a similar type in young and adults	Effects at lower doses and/or shorter latency than in adults	Effects at similar dose and/or similar latency as in adults	No effects or effects at higher doses and with longer latency than in adults
Dose response nature of the experimental animal data	Dose-related incidence of response	Incidence and intensity of response increases with dose		Effects only at high doses and secondary to generalized toxicity
	Relative potency of response	Effects at several doses including those lower than adult toxicity	Effects only at highest dose and minimal/low adult toxicity	Effects only at highest dose; clear adult toxicity at or below that dose
	Slope of the dose response curve ⁸	Very steep or very shallow curve		Intermediate slope
	Definition of the NOAEL or BMD	Poor; e.g. no NOAEL, no experimental doses in the range of the BMD	Moderate; e.g., LOAEL, only two doses, experimental doses in the range of the BMD	Good; e.g., NOAEL, several doses, some in the range of the BMD
Relevance of the experimental animal data to humans	Toxicokinetics	Evidence suggesting similar qualitative and quantitative metabolism in humans		Evidence suggesting that the metabolic profile differs in important aspects between animal model and humans
	Biological response	Same types of effects in more than one species	Different types of effects in more than one species	Effects seen in one species, but not in others
	Mechanism-of-action studies	Demonstration of homologous mechanism of action in animal model and humans		Evidence suggesting the mechanism of action is species-specific and irrelevant to humans

⁷Assumes a sufficient database as described in EPA (1991, 1996).

⁸See text for discussion of this criterion.

Issue #1: Human Data on Pre- and Postnatal Toxicity

Adequate human data are the most relevant data for assessing the potential for effects in humans. When sufficient human data are available to judge that an adverse developmental outcome is clearly related to exposure, the degree of concern is high. Sufficient data to show that there are no effects are more difficult to obtain because they usually require more data and evaluation of a wide range of endpoints. Sufficient data to judge that exposure to a pesticide does not cause pre- or postnatal toxicity would lead to a low degree of concern. Criteria for sufficiency of data are indicated in the EPA's 1991 developmental toxicity and 1996 reproductive toxicity risk assessment guidelines (EPA, 1991; EPA, 1996).

Issue #2: Pre- and Postnatal Toxicity in Animal Studies

The nature of pre- and postnatal toxicity relative to adult toxicity impacts the degree of concern. Two generalizations can be made about the endpoints of developmental toxicity: 1) when exposure occurs during early embryonic development and/or critical stages of organogenesis at the gross or histological level, the nature and consequences of the outcome may be very different from the outcome experienced by an adult; and 2) when exposure occurs after organ systems of a child have sufficiently developed and matured to be functional, the toxic outcomes that result are likely to be more similar to those experienced by an adult although the degree of response may be different; they may have a different latency before the adverse effect develops, and/or they may have long-term consequences that are greater or lesser than in adults. Data on adults to be used in comparison with developmental effects in the young should come not only from the reproductive and developmental toxicity studies, but should be evaluated in the core data set as a whole. In particular, the acute, short-term, and subchronic toxicity (including neurotoxicity and immunotoxicity) studies can be compared with the prenatal developmental toxicity study. The subchronic toxicity studies are a source of adult toxicity data to be used in conjunction with the adult data from the two-generation reproduction study for comparison with developmental effects seen in this study.

As indicated in Table 4, the degree of concern would be highest when data from sufficient animal studies show: either developmental effects of a different type than are seen in adult studies, or developmental effects of a type similar to those seen in adults, but occurring at doses lower than those causing effects in adults. When developmental effects of either type are seen at similar dose levels as those in adults, the degree of concern would be moderate. The degree of concern would be lower when: no developmental effects are seen; developmental effects are seen only at higher doses than in the adult; or effects are judged to be minor or secondary to generalized toxicity or have a longer latency than in the adult.

Issue #3: Dose Response Nature of the Experimental Animal Data

The dose response nature of the experimental data also impacts the degree of concern. For example, when data are **dose-related**, that is, the incidence and intensity of response increases

with increasing dose, the degree of concern would be greater than if effects are seen only at very high doses and information is available to show that they are secondary to more generalized toxicity. Also, the **relative potency** of the response may impact degree of concern; if developmental effects are seen at several doses including those at lower doses than for adult toxicity, the degree of concern will be much greater than if clear adult toxicity is shown for doses at or below the developmentally toxic dose. The **slope of the dose response curve** is of concern when either a very steep or very shallow curve occurs. As noted below, however, the concern is related to the anticipated exposure levels. For example, if exposure is anticipated to be significant for children, a very steep dose response curve would be of greater concern because a small increment of increase in exposure level could increase the response rate dramatically. A very shallow dose response curve also may be of concern because there is less certainty about the shape of the dose response curve at lower dose levels, and thus identification of the level below which there would not be expected to be any effect (i.e., the biological threshold). Finally, if **definition of the NOAEL or BMD** is poor, i.e., there is no NOAEL or the increment between the LOAEL and NOAEL is very large, or there are no experimental doses in the range of the BMD), the degree of concern is higher than in the case where the NOAEL or BMD is well-defined.

Issue #4: Relevance of the Experimental Animal Data to Humans

The Agency's risk assessment guidelines for developmental and reproductive endpoints indicate as one of the major default assumptions that animal data are relevant for humans. Such defaults are intended to be used only in the absence of experimental data that can provide direct information on the relevance of animal data. The advent of physiologically-based pharmacokinetic models and biologically-based dose response models provides a framework for incorporating mode of action data into the risk assessment process, and thus allows movement away from the default considerations.

Several types of information can be considered in determining the relevance or non-relevance of effects observed in animal models for humans. This information is utilized in a variety of ways, from determining the role of metabolism in toxicity (e.g., Is the parent chemical or a metabolite responsible for the toxicity? Are they common to both animals and humans?) to assessing whether homologous activity would be expected across species (e.g., Do humans share the sensitivity of the animal model, or is the response due to some species-specific idiosyncratic reaction?) to the basic determination of whether or not a threshold is likely to exist for the response (e.g., Are repair mechanisms capable of maintaining a homeostatic process?) to lending credence to the criteria of biological plausibility in evaluation of the epidemiological evidence (e.g., Does the exposure window match the known critical period for the key developmental process?) All of this information must be weighed in light of the known heterogeneity of the human population versus relatively homogeneous, inbred strains of laboratory animals used in toxicity testing studies and housed under carefully controlled environmental conditions.

The availability of data that can be used in determining the relevance of a toxicology data

set to humans can have a major impact on degree of concern although such data are often outside the range of the core toxicology data set as defined above. For example, comparative **toxicokinetic** data in animals suggesting qualitative and quantitative metabolism similar to that in humans would result in a higher degree of concern than would the absence of such comparative data. On the other hand, toxicokinetic evidence suggesting that the metabolic profile differs in important aspects between the animal model and humans could result in low or no cause for concern.

Similarities in **biological response** in more than one species could also result in a higher degree of concern for humans, even if such data were not available in humans. In contrast, response data showing effects in one species, but not others, might result in a lower degree of concern, but would need to be balanced by what is known about toxicokinetics and mechanism of action in humans.

Mechanism of action information is also important in understanding whether a particular effect is adverse or not. For example, a transient reduction in anogenital distance in the postnatal animal following perinatal exposure is more significant if the chemical is also known to be an anti-androgen. Likewise, the interpretation of increased skeletal variants observed following exposure to many chemicals would be enhanced by data indicating the mechanistic pathways for these agents and defining the overall biological significance. Mechanism-of-action data are also important in determining whether various chemicals work by common mechanisms of action which would then be considered in a cumulative risk assessment.

The Toxicology Working Group noted that some aspects of degree of concern currently are taken into account in the RfD process. For example, human and animal data are considered currently in the process of calculating acute and chronic RfDs. Furthermore, the Working Group noted that when the data indicate developmental effects are the most sensitive or critical effects, and appropriate uncertainty factors are applied to the NOAELs for these developmental effects to calculate the RfD(s), there would normally be no need for an additional uncertainty or modifying factor or an FQPA Safety Factor to address potential pre- and postnatal toxicity. Finally, the Toxicology Working Group has suggested that should any residual uncertainties regarding degree of concern remain after all appropriate uncertainty factors have been applied, these residual uncertainties could be accommodated by the use of an additional modifying factor when deriving the RfD(s) for the pesticide.

3. The OPP Policy with Respect to the Degree of Concern for Potential Pre- and Postnatal Toxicity

OPP is adopting the framework for judging the degree of concern for potential pre- and postnatal toxicity outlined by the Toxicology Working Group of the Agency 10X Task Force, as well as most of the specific recommendations about how specific factors should be handled. Thus, OPP is expanding its consideration of factors to include the four categories identified in the Toxicology Working Group's report: human data on pre- and postnatal toxicity; pre- and

postnatal toxicity in animal studies; the dose response nature of the experimental animal data; and relevance of the experimental data to humans. OPP also agrees with the Toxicology Working Group that all of this information should be considered together in making a weight-of-the-evidence judgment about the overall degree of concern about the potential for pre- and postnatal toxicity.

OPP does not, however, agree with another aspect of the Working Group's recommendations. This is that the degree of concern should be addressed only when establishing the RfD(s) for a pesticide, for example, by using an additional modifying factor, along with the appropriate uncertainty factors, to derive an RfD. OPP agrees that many of the circumstances which would help characterize the degree of concern are implicitly addressed when an RfD is established using the NOAEL from developmental studies or studies conducted with juvenile animals. In some cases, however, there may still be residual uncertainties. For example, neither OPP nor the Agency risk assessment process currently takes the steepness of the dose response curve into account in setting RfDs for chemicals. Because there is no formal procedure for applying this or the other factors that are presented in Table 4 and no general agreement on the appropriate size of uncertainty and modifying factors, OPP believes it is more appropriate to consider any residual concerns about the potential for pre- and postnatal toxicity during the decision about the FQPA Safety Factor. Until such time as consensus has been achieved in the scientific community, OPP will continue to handle any residual concerns about degree of concern, after the RfD has been derived, in the FQPA Safety Factor decision process, by recommending that an additional factor be retained, if a significant degree of concern exists.

Furthermore, OPP has decided, as a policy matter, that it will continue, during the FQPA Safety Factor decision process, generally to apply an FQPA Safety Factor greater than 1X when infants and children appear to be the most sensitive age group in the population, particularly when there is a high degree of concern for the potential for pre- or postnatal effects. This decision rests in part on the fact that, during the time necessary to make a transition to the more expansive data requirements described in Section V.A., OPP will not have the complete core toxicology data set recommended by the Toxicology Working Group to evaluate potential pre- and postnatal toxicity. As discussed above, the absence of such data would be considered, by itself, as the possible basis for applying either an additional database uncertainty factor or an FQPA Safety Factor. When such data are missing, and available information indicates that infants and children appear to be more sensitive than adults, OPP would be particularly concerned. Until there is a better scientific understanding of this type of toxicity, OPP believes there is a greater chance that a chemical, which is both particularly toxic to infants and children and not fully tested, may turn out to be more toxic than indicated from a limited data base. Thus, OPP concludes that there should be extra protection in the form of an additional FQPA Safety Factor greater than 1X. The size of the FQPA Safety Factor would depend on the nature of the effects observed and the difference in apparent sensitivity. Such decisions should be made in connection with the overall examination of the residual uncertainties and the application of other uncertainty and safety factors.

VI. CONSIDERATIONS RELATED TO THE UNDERSTANDING OF THE POTENTIAL FOR EXPOSURE TO INFANTS AND CHILDREN

This section will describe the factors/issues related to exposure assessment and the completeness of the exposure database that must be considered when making an FQPA Safety Factor finding.

A. What Constitutes a Complete and Reliable Exposure Database for a Food-use Pesticide When Assessing Aggregate Risk to Infants and Children?

Just as is true for hazard potential, the completeness and reliability of the exposure database for food-use pesticides, in the context of aggregate risk assessment, is a primary consideration relative to the FQPA Safety Factor decision. Again, an analysis should be performed for each pesticide, using a weight-of-the-evidence approach, in order to determine the completeness and reliability of the exposure database for that pesticide, as determined directly, or as determined indirectly through the appropriate use of sufficiently conservative assumptions. This analysis should address all important sources, routes and pathways of exposure for the pesticide and include both the expected exposure duration as a consequence of each use and the expected pathway(s) of exposure.

Additionally, the analysis should identify the population groups (including age groups) that are at the greatest risk from aggregate pesticide exposures. This should include identifying those groups with the potentially highest exposure as well as the greatest susceptibility to the exposure. Ideally, so as to not overestimate exposure unnecessarily, the aggregate exposure assessment should use probabilistic multimedia, multiroute and multipathway models to develop population exposure distributions.

A determination of the level of confidence one has in a chemical's existing exposure database will be made as preparation for making an FQPA Safety Factor decision. A simple qualitative scale from "high" to "low" is useful for this purpose. A *high level of confidence* determination reflects the judgment that the assessment is either highly accurate or based upon sufficiently conservative input that it overestimates those exposures that are critical for assessing the risks to infants and children. A determination of *low level of confidence* would represent that the assessment was inadequate to judge whether or not exposure was overestimated, underestimated or accurately estimated. The determination of the level of confidence must be made on a case-by-case basis.

The data sources that are used currently to estimate exposures to pesticides in the diet (i.e., food and water) and from use in residential and similar settings (e.g., schools, parks, offices) are described below.

1. Dietary

a. Food

40 CFR 158.240 sets out the residue data requirements (both Tier 1 and Tier 2, triggered) for “conventional chemical” food-use pesticides. All of these assist in the understanding of the potential for exposure to pesticide residues resulting from consumption of food. They include:

- 1) Nature of the residue in plants (i.e., the crop that becomes a human food source)
- 2) Nature of the residue in animals (when the animal is a human food source)
- 3) Magnitude of the residue
 - a) Crop field trial data
 - b) Processed food/feed (if the crop is a food source for an animal which is a human food source)
 - c) Meat/milk/poultry/eggs (if an animal is fed the treated crop and it is a human food source)
 - d) Potable water (if the use is aquatic)
 - e) Fish (if the use is aquatic)
- 4) Reduction of residues (resulting data provide more accurate estimate of residues in food, as eaten).

These data along with food consumption data from the USDA consumption surveys, and sometimes from other sources and data on actual use of pesticides (“percent crop treated”) provide the basis for a food exposure assessment. Acute and chronic dietary exposures to pesticides in foods are estimated using indirect modeling approaches that consider pesticide residues in the food and the amount of food consumed. OPP traditionally has used *deterministic* assessments involving point estimates of specific parameters to generate a single estimate of exposure and risk based on various assumptions about the concentration of pesticide residue in the food. More recently, the Agency has developed draft guidelines for the preparation and review of *probabilistic* exposure assessments. Probabilistic techniques can enhance risk estimates by more fully incorporating available information concerning the full *range* of possible values that each input variable could take such as the variability and uncertainty in pesticide concentrations in air, water, soil, or in exposure factors. Probabilistic exposure assessment models combine these distributional data using numerical methods and algorithms that link route- and pathway-specific concentrations with exposure factors, human activity data, or consumption survey data. These models also allow for the prediction of inter-individual variability in the population exposures and uncertainties associated with the various percentiles (e.g., greater than 75th or 90th percentile) of the predicted exposure and dose distributions.

In an attempt to conserve limited resources, OPP assesses exposure in food using a tiered approach, proceeding from conservative to more refined assumptions as the risk management situation requires. Assessments usually begin with worst-case assumptions (for example, residues on foods at tolerance levels and 100% crop treated). Food exposure estimates based on “worst-

case” assumptions are designated as the Theoretical Maximum Residue Concentration (TMRC). They can then be refined using more realistic values for pesticide residues (for example, using average residues from field trials or monitoring data, actual percent crop treated data and results from processing and cooking studies) to produce better estimates of pesticide residues in food at the time of consumption.

Use of commonly available pesticide residue data sets and underlying assumptions generally result in conservative food exposure estimates for infants and children. Uncertainties associated with these exposure estimates are not readily quantifiable and are usually characterized in qualitative terms. The Agency is working to develop more accurate assumptions and residue data sets to reduce uncertainties associated with current data sets.

Tolerance level residues used in Tier 1 dietary exposure estimates are not expected to accurately reflect actual residues in ready to eat foods; rather they are intended to provide inputs for “worst-case” exposure estimates. More accurate or realistic exposure assessments require more accurate prediction of pesticide residues in foods as they are consumed. Unfortunately, most residue studies are designed for purposes other than estimating food exposure, and as such, continue to introduce conservative uncertainties or bias into the assessment.

The risk assessor needs to be cognizant of the possible limitations of the food consumption data that are utilized in preparing dietary exposure assessments. Surveys currently accepted by the OPP as sources for estimating food consumption by individuals are the USDA Nationwide Food Consumption Survey (NFCS) 1977-78, the Continuing Survey of Food Intakes by Individuals (CSFII) 1989-91, and the CSFII 1994-96. These surveys were designed to USDA conducts the surveys to monitor food use and food consumption patterns in the US population. The data were collected as a multi-stage, stratified, probability sample that was representative of the 48 contiguous states. These surveys consist of food consumption data obtained over two or three days based on questionnaires completed by consumer. The most recent survey (CSFII 1994-1996) was designed to obtain a sample that would provide equal precision over all sex-age domains. The data are used by a number of federal and state agencies to improve understanding of factors that affect food intake and the nutritional status of the US population.

However, OPP does *not* consider these data adequate to model *chronic* consumption patterns as distributions across the population, but does find them appropriate and adequate for use in deterministic exposure assessments. Demographic information collected as part of the surveys allows classification of food consumption information by categories such as ethnic subgroups contain too few people to develop meaningful consumption distributions for consumption patterns unique to those subgroups. The members of these subgroups occur in other groupings of the population such as General US Population and Children (1-6 years). Care must be taken when determining what foods drive an unacceptable exposure assessment to ensure that ethnic foods are not of concern. This consideration is important in ensuring that potential risk to subpopulations is not overlooked. Even though the populations surveyed were large, demographic categories have not been demonstrated to contain a sufficient number of short-term

consumption estimates to develop meaningful distributions for food items that have a low probability of being consumed. This was recognized in 1993 in the NRC/NAS report, Pesticides in the Diets of Infants and Children. Since then, a supplementary survey that will provide more robust data for young children has been conducted. Review and analysis of the survey results are now underway.

For acute consumption for infants and children, the NSCF and CFSII surveys provide adequate, high quality data to model distributional patterns. An estimated 1900 data points are required to produce an estimate of consumption that is accurate to the 95th percentile. Using these data, the Agency currently addresses total population and subpopulation risk for a variety of age groups, such as infants, children 1-6 years of age, and children 7-12 years of age. Such age clustering is performed to increase the total observations to sufficient number to allow a sample size that will achieve the target value. For infants <1 year of age, the number of observations available is somewhat less than the target sample size. However, because infants consume a less varied diet than older portions of the population, the results are less sensitive to the lower sample size and are consistent with the target samples estimated by the survey designers to be necessary to describe the diets of infants.

b. Drinking water

For each use of a food use pesticide, an assessment of its potential to find its way into drinking water sources or supplies must be made. 40 CFR 158 data requirements include:

- 1) Magnitude of the residues in potable water (aquatic use)
- 2) Degradation studies-lab
- 3) Photodegradation in water, soil and air
- 4) Metabolism studies in soil and water (depending upon use site)
- 5) Mobility studies on leaching and adsorption/desorption, and volatility
- 6) Dissipation studies in the field on soil (terrestrial use) and sediment (aquatic use)
- 7) Prospective groundwater monitoring study

Data from these studies, sometimes along with monitoring data in raw and finished drinking water from a variety of sources, and data on water consumption by humans, are combined in a variety of ways in one or more models which provide a perspective on whether or not the pesticide will or could occur in drinking water and an estimate of the level of occurrence. As with the food exposure assessment process, the drinking water analyses are tiered, and result in more refined estimates of exposure as the analyses proceed through the tiers.

OPP scientists use pesticide-specific data as inputs to “screening level” models (GENEEC and PRZM/EXAMS for surface water and SCI-GROW for groundwater). These models allow development of rough estimates of pesticide concentrations in surface water and groundwater. The models are based on 20-plus years of experience in studying how pesticides move in the

environment and are based on a good understanding of the key characteristics of pesticides which determine where they are likely to move in the environment. OPP views the estimates coming out of these models as upper bound estimates of potential pesticide concentrations in drinking water. During this stage of the process, OPP reviews in-house water monitoring data to check to be sure that the screening level estimates are in fact “upper bound” estimates. If OPP finds that monitoring data suggest the possibility of higher concentrations in surface or groundwater than these models indicate, OPP moves to a more thorough analysis of available monitoring data.

Comparisons of the model estimates (which OPP views as upper bound estimates of potential pesticide levels in drinking water) are then made to human health-based “drinking water levels of comparison” or “DWLOCs” (after having first considered all food-related and residential exposures). Based on this comparison, the pesticide is cleared as a potential risk from a drinking water perspective or attempts are made to refine the estimates of pesticide concentrations in order to make them less worst-case and more realistic.

If the determination is made that refinements of these estimates are needed, additional water monitoring data are gathered and additional analyses conducted. Typically, OPP consults the United States Geological Survey (USGS) National Water-Quality Assessment Program (NAWQA Program) and the National Stream Quality Accounting Network (NASQAN), the Office of Water’s STORET data base, the data from the USGS Mid-Continent Group, OPP’s Pesticides in Groundwater Data Base, and the National Pesticide Survey to identify monitoring data. In some cases, OPP also has done open literature searches or has contacted state agencies to obtain additional water monitoring data. OPP generally defers doing an intensive analysis of available monitoring data until after it completes its comparison of the upper bound drinking water estimates to the human health levels of comparison (DWLOCs) because locating, analyzing and interpreting water monitoring data, for purposes of developing a refined estimate of drinking water levels can be very time consuming. In at least 50% of the cases to date, OPP’s model estimates have been sufficient to clear pesticides from concern and further refinement has not been necessary.

If monitoring data are available and reliable, review of the existing data and other available information (i.e., sample collection and analysis) is made such that the full characterization of the range of values reported, the highest values reported, the 95th percentile value, and the mean value can be addressed. If these data are adequate to produce some regional-based picture of the distribution of measurements, this analysis is completed as well.

OPP carries out exposure assessments which are appropriate for the specific endpoints of concern, i.e., short-term (for acute effects) and/or longer-term average (for chronic effects or cancer) drinking water concentrations are estimated. Based on this analysis and characterization of monitoring data followed by integration with food and residential exposure analyses, aggregate exposure assessments can be completed.

2. Residential and Other Non-occupational Exposure

When compared with the number of studies required in other areas of risk assessment such as toxicology or dietary exposure, the number of studies required in 40 CFR 158 which assist in the understanding of “residential” exposure to infants and children is small. In addition, none of these are Tier 1 studies. That is, all must be triggered based upon the results of the toxicology studies, and identification of the expected pathways of exposure. The existing conditional or triggered data requirements include:

- 1) Foliar dissipation
- 2) Soil dissipation
- 3) Dermal exposure (unless surrogate data are available)
- 4) Inhalation exposure (unless surrogate data are available)

Even though chemical-specific data are sparse, adequate and sufficiently conservative residential exposure assessments can be conducted for infants and children. Data required under FIFRA, along with environmental and biomonitoring data from a variety of sources coupled with data on human activity patterns and biological factors such as body weights, body surface, etc., constitute inputs to models which can provide estimates of exposure. A complete exposure assessment should consider all of the important exposure routes and pathways (e.g., pesticide residues on hard surfaces, transfer to skin via dermal contact, exposure not resulting directly as a consequence of an approved use as a pesticide) for infants and children.

Given the fact that there is a paucity of chemical-specific empirical data for use in direct methods for residential exposure assessment, an indirect deterministic modeling approach is currently being used. This approach is documented in the draft “Standard Operating Procedures (SOPs) for Residential Exposure Assessments” (OPP, 1997). The objective of these SOPs is to provide high-end screening level methods (models and exposure factors) for developing Tier 1 residential assessments for both handler and postapplication exposures; the outcomes are considered to be conservative estimates. Additionally, the SOPs are intended to identify the important residential exposure scenarios for young children. Each SOP provides procedures for estimating short- and intermediate-term or acute daily doses for a single route and pathway of exposure. Exposures from each residential and other nonoccupational setting can then be aggregated to estimate total exposure. Each SOP includes: a description of the exposure scenario, the recommended methods (i.e., algorithms/models and exposure factors) for quantifying doses, sample calculations, limitations and uncertainties associated with the use of the SOP, and references. The draft SOPs were peer-reviewed by the FIFRA Scientific Advisory Panel (SAP) in September, 1997, and have recently received public notice and comment review. They are being revised on the basis of these comments. Important aspects of the revisions are an identification of all of the important pathways and routes of exposure, as well as an update of exposure factors to be used in the algorithms. The revised SOPs will be available later this year.

B. How the Approaches for Assessing Single Exposure Route/pathways (Food, Drinking water, and Residential and Other Non-occupational Exposures) Compensate for Database Deficiencies in the Understanding the Potential for Exposure to Infants and Children via Each of These Routes/Pathways

At the present time, OPP is developing assessments that reflect only those exposures resulting as a direct consequence of an approved or requested use of a pesticide. These fall into three categories: food, drinking water and residential. In fact, the term “residential” may be somewhat misleading because this definition encompasses more exposure scenarios than that term would indicate. It also includes exposures that would arise from the use of pesticides in schools, day care centers and other more public spaces.

As OPP gains experience in conducting aggregate risk assessments, the methodologies evolve and the awareness of other possible sources of exposure matures, OPP is expanding its aggregate (and cumulative, when appropriate) risk assessments to include scenarios that do not represent exposures which are the direct consequence of an approved pesticide use (e.g., non-pesticidal uses of a commodity chemical in a consumer product or as a pharmaceutical.)

1. Dietary

a. Food

Current food assessment approaches would tend to reflect a *high level of confidence* when pesticide-specific data are adequate and complete (i.e., food consumption patterns for infants and children are well understood and residue databases on actual foods consumed are adequate), if conservative assumptions are used, and if models are used that reflect high-end exposures and adequately compensate for the lack of empirical data through use of assumptions, which themselves are based upon reliable data. For food exposure assessments in which data are incomplete, it may lead to underestimation or overestimation of dietary exposure. In some of these cases, the default assumptions and models employed may not be conservative enough to ensure confidence that exposure to infants and children is not underestimated and, thus, would lead to an interpretation of a *low level of confidence* in the exposure assessment.

b. Drinking water

An assessment can be developed that has a *high level of confidence* even if pesticide-specific data (e.g., monitoring data) are incomplete if conservative assumptions are used and models are used that reflect high-end exposures through the drinking water pathway. For drinking water assessments in which data are incomplete and/or for which the default assumptions may not be conservative enough to ensure confidence that exposure to infants and children is not underestimated, there would be a *low level of confidence*.

OPP views the estimates of drinking water exposure derived in the application of its

current approaches for drinking water assessment (a combination of models and default assumptions, based upon reliable data) as upper bound estimates of potential pesticide concentrations in drinking water. As such, they generally yield assessments having a *high level of confidence* that they are sufficiently conservative to adequately protect infants and children via this pathway.

2. Residential and Other Non-occupational Exposure

The non-occupational, residential exposure assessment procedure currently is based on the indirect modeling approach. Hence, to have a *high level of confidence* that the exposure assessment is protective of infants and children, exposure factors and models that are conservative must be used. This determination can be made even in cases where the pesticide-specific empirical data are lacking or incomplete, if conservative assumptions are used to determine high-end exposure scenarios that compensate for the paucity of chemical-specific empirical data. The Tier 1 residential exposure assessments for short-term exposures generated by the SOPs generally appear to meet this requirement. If, on the other hand, for exposure scenarios in which data are incomplete, or certain of the known exposure scenarios have not or cannot be addressed currently, and for which the default assumptions may not be conservative enough to ensure confidence that exposure to infants and children is not underestimated, there is a *low level of confidence*. In these cases, these inadequacies would be taken into account by incorporating an additional safety factor during the FQPA Safety Factor decision process.

It should be understood, however, that because not all exposure scenarios are included in the SOPs, each pesticide-specific exposure assessment must be evaluated on a case-by-case basis. This approach will ensure that those scenarios that produce the highest exposure and dose estimates have been included and the entire assessment is sufficiently conservative to protect infants and children. In spite of the fact that there is uncertainty around many of the exposure factors, the overall exposure estimates being used can be viewed as sufficiently conservative. Essentially, the draft residential SOPs for short-term exposures mirror the strategy for creating reasonable high-end scenarios as indicated in the EPA's Dermal Exposure Assessment: Principles and Applications (EPA, 1989a). The specific guidance from this document is as follows:

“The strategy for selecting default values is to express them as a range from a central value to a high end value of their distribution. Where statistical distributions are known, the central value corresponds to the mean and the high end value corresponds to the 90 or 95th percentile. Where statistical data are not available, judgement is used to select central and high end values. This strategy corresponds to the default selection strategy used in the Exposure Factors Handbook (EPA, 1989b). Note that the range of values is intended to represent variations that occur across a population. Ideally, assessors should also consider uncertainty in the actual value due to measurement error or other factors. The combination of these factors to derive an exposure estimate can create scenarios of varying severity. Ideally, these combinations would be made via statistical techniques such as Monte Carlo Analysis. However, this requires detailed knowledge of

the distributions of each input variable, which is rarely available. Lacking such data, some general guidance can be offered as follows: use of all central values for each parameter should produce a central value scenario; use of all high end values for each parameter, produces a bounding estimate that is usually above the high end of the distribution; and a mix of high end and central values is probably the best way to create a reasonable high end scenario.”

C. How the Proposed Approach for Assessing Aggregate Exposures Compensates for Exposure Database Deficiencies in the Understanding the Potential for Exposure to Infants and Children

Traditionally, OPP’s exposure assessments have been focused on a single chemical and single route of exposure. Exposures and resultant risks were expressed individually, not as combined exposures or risks, except for dietary exposure in food. FQPA mandates consideration of aggregate exposures to pesticides from food, drinking water and all other non-occupational sources for which reliable data exist. The aggregate exposure approach that is being used most often at the present time is to sum the single point estimates for each exposure source. This is very conservative for two reasons. First, the estimate for each source is conservative because it is based on high-end exposure assumptions. The aggregate or summed exposure should, therefore, be conservative. Second, the practice of summing the single point estimates for each source assumes that an individual will not only receive an exposure from all sources, but a high-end exposure from all sources. Based on this very conservative approach, there should be a high level of confidence in these exposure assessments that they are protective of infants and children.

A document entitled “Interim Guidance for Conducting Aggregate Exposure and Risk Assessments” (OPP, 1998) provided an initial foundation for combining risks by route, but it was acknowledged that additional work was needed to refine exposure and characterize important exposure information and pathways specific to infants and children, and to further develop the methods for aggregating the routes/pathways. Current methods for aggregating exposures primarily use simple addition and do not account for the distribution of exposure and risk across the population; they only provide bounding point estimates.

In February, 1999, a draft document entitled “Guidance for Performing Aggregate Exposure and Risk Assessments” (OPP, 1999) was discussed at a FIFRA Scientific Advisory Panel meeting. Among the topics presented was acknowledgment of the desirability and need for the development and use of probabilistic techniques, instead of, or in addition to, the existing deterministic methods. A two-stage Monte Carlo simulation system was proposed to be used in the probabilistic pesticide exposure /dose model. Both the uncertainty in each model parameter and the variability in the concentrations or exposure factors are explicitly simulated with this new procedure. Acute, as well as short-term, intermediate-term, and chronic average exposures/dose to selected pesticides eventually can be predicted based on various scenarios of pesticide use. The model’s outputs will provide information on estimates of both inter-individual variability in the population exposure/dose, as well as uncertainty in the predicted percentiles of the age and gender-specific empirical pesticide exposure/dose distributions.

VII. INTEGRATION OF THE STATUTORY REQUIREMENT WITH THE CURRENT RISK ASSESSMENT PROCESS

This section of the policy summarizes the above discussion and focuses on how the requirement for the FQPA Safety Factor is integrated into OPP's current risk assessment process. It discusses the circumstances in which OPP would exercise its discretion to use the default 10X Safety Factor or a different safety factor because OPP believes that such factors are necessary to assure that the risks to infants and children from pesticide exposure are adequately assessed. Further, this section explains that because OPP often establishes different Reference Doses for different exposure time frames, the analysis of the need for the FQPA Safety Factor may be conducted more than once for a particular pesticide and the decisions may differ from one another. Finally, this section clarifies the terminology that will be used in describing if and how the levels of exposure that are found meet the statutory standard of "a reasonable certainty of no harm."

A. OPP Principles for Integrating the FQPA Safety Factor Analysis with the Current Risk Assessment Process

The starting point for analysis of the FQPA Safety Factor begins with the statutory provision. As discussed above, the additional 10X Safety Factor under FQPA is intended to take into account three specific dimensions of the evaluation of the potential risks to infants and children:

- the completeness and reliability of the toxicology database,
- the potential for pre-natal and postnatal effects,
and
- the completeness and reliability of the exposure database.

The statute further provides that OPP may use a different safety factor if it determines, based on reliable data, that the resulting margin of safety is adequately protective of infants and children.

As discussed in more detail in Section III of this policy document, OPP interprets the statutory provision to require the use of the default 10X safety factor, in addition to the standard 100X for potential intra- and inter-species differences when animal data form the basis for the hazard values (i.e., RfDs), unless it has reliable data to justify a different safety factor. Thus, consideration of using a different safety factor must take into account the information available on each specific pesticide and must necessarily be made on a weight-of-the-evidence basis.

B. Scope of the FQPA Safety Factor Analysis

As Section III makes clear, it is important that OPP avoid "double counting" safety/uncertainty factors, that is, using a factor at more than one stage of its risk assessment for a pesticide to account for the same type of uncertainty. Therefore, at the integration stage of its

analysis, OPP is focused on determining whether residual concerns remain about the way in which the risk assessment process handled the three dimensions of the FQPA Safety Factor. Section V describes the degree to which the three dimensions of the risk assessment related to the FQPA Safety Factor have been, and will be, addressed as part of the current hazard characterization and exposure assessment processes. The discussion below summarizes the current process and then explains where the current process may not have addressed fully the three dimensions of the risk assessment specifically covered by the FQPA Safety Factor.

The first dimension, the completeness and reliability of the toxicology data base, is addressed in two stages of the risk assessment process -- indirectly in the discussion of what constitutes the core toxicology database for an individual pesticide and more directly in the determination of the need for a database uncertainty factor. As explained above, the description of the types of data that would generally be required for a conventional food-use pesticide does not mean that every pesticide which is missing one or more of the required studies does not have a sufficiently complete toxicology database for the purpose of evaluating the potential for hazard to infants and children. Conversely, OPP might also conclude that a pesticide – for which there are data on each type of study required in the core data set – does not have a sufficiently complete toxicology database. In other words, consideration of the completeness of the database must take into account not only what studies may be missing, but also what information is already available about the pesticide. Therefore, the determination of the completeness of the toxicology database should initially be considered at the stage where OPP makes its decision about the use of a database uncertainty factor, that is, in the development of the RfD(s). To a large extent, the database uncertainty factor analysis will address the first dimension of the FQPA Safety Factor provision.

As explained in Section V, OPP's default position is that a database uncertainty factor will always be applied when the toxicology database lacks one or more of the following types of studies:

- a two generation reproductive toxicity study;
- two developmental toxicity studies (in different species); and
- two chronic toxicity studies (in the rodent and nonrodent)

Although OPP intends to expand its data requirements to include additional types of studies, with early emphasis on the adult acute and subchronic neurotoxicity study, the adult immunotoxicity studies, and the developmental neurotoxicity study, the absence of these additional studies will not automatically be the basis for imposition of a database uncertainty factor. OPP does, however, plan to consider the application of a database uncertainty factor greater than 1X, if the subchronic neurotoxicity study in adult rats has been requested for certain conventional chemicals, but the data have not yet been generated, reviewed and incorporated into the hazard assessment for those specific chemicals. For the other studies, OPP will need to consider whether the absence of these data warrants imposition of the database uncertainty factor, the default 10X FQPA Safety Factor or some different safety factor.

Some aspects of the second dimension of the risk assessment related to the FQPA Safety Factor, the potential for prenatal and postnatal effects and the degree of concern associated with that potential, currently are taken into account in the RfD derivation process. For example, human and animal data are currently considered in the process of calculating acute and chronic RfDs. When the data indicate that developmental effects are the most sensitive or critical effects, appropriate uncertainty factors are applied to the NOAELs for these developmental effects to calculate the RfD(s). However, there is no formal procedure for applying all of the criteria and factors that are presented in Table 4 in determining the degree of concern for pesticides. The Toxicology Working Group has recommended that a additional, modifying factor be incorporated along with the appropriate uncertainty factors into the RfD-setting process to accommodate for any residual uncertainties. Until consensus on such an approach has been achieved in the scientific community, OPP will continue to incorporate its findings about degree of concern, in part, during the RfD derivation process, but also in the FQPA Safety Factor decision process, by recommending that some additional safety factor be applied, if a significant degree of concern exists and all of the issues have not been adequately addressed during hazard characterization.

The third aspect of the risk assessment process related to the FQPA Safety Factor, the completeness and reliability of the exposure database, is addressed currently through the use of conservative default assumptions. As discussed in Section VI, OPP's practice is to use models and data which are very conservative, i.e., the resulting estimates almost certainly overstate exposure, and therefore, OPP generally has high confidence that its exposure assessments provide ample protection for children and infants. To the extent, however, that specific routes, pathways, or durations of exposure are inadequately assessed, then OPP would need to consider imposing either the default 10X safety factor or a different safety factor.

Finally, whenever a decision is made to use either the default 10X safety factor or a different safety factor to address these dimensions of the risk assessment process, such a factor is used to determine the adequacy/acceptability of the estimated/calculated margin of exposure, NOT to revise the RfD or equivalent hazard value. This step is now being described as calculation of the Population Adjusted Dose (PAD), which is the RfD, or equivalent hazard value, divided by the FQPA Safety Factor for that population.

For each aggregate risk assessment conducted for a single active ingredient, there may be more than one FQPA Safety Factor decision made, and they may be different from one another. Separate decisions may be necessary for 1) different population(s) being evaluated, and 2) different durations of exposure (e.g., acute, short-term/intermediate, long-term). Separate decisions will not be made for each different exposure scenario included in a single aggregate assessment. The decision(s) should be based upon a weight-of-the-evidence evaluation of the certainties and uncertainties in that aggregate assessment as a whole, and a single conclusion reached for the population and duration of exposure that is the focus of the assessment. With this approach, examples of FQPA Safety Factor decisions that might be necessary to make are:

- 1) One each for one or more age groups of infants and children for up to three durations of exposure.
- 2) One each for women of child-bearing age for up to three durations of exposure, if toxicity as a consequence of exposure to the fetus during pregnancy is of concern.
- 3) (Rarely) One each for sexually mature males for up to three durations of exposure, if it has been shown or would be expected that exposure to the male may lead to adverse consequences for the conceptus.

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