DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) IN TOLERANCE ASSESSMENT

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EXECUTIVE SUMMARY

On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law, significantly amending the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). Among other changes, the new law provides heightened protections for infants and children, directing EPA, in setting pesticide tolerances, to use an additional tenfold margin of safety to protect infants and children, taking into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases. The statute authorizes EPA to replace this tenfold "FQPA safety factor" with a different FQPA factor only if reliable data demonstrate that the resulting level of exposure would be safe for infants and children.

EPA established a Task Force of senior scientists, knowledgeable in the fields of hazard and exposure assessment, to help it identify the types of information that would be appropriate for evaluating the safety of pesticides for infants and children. The Task Force included representatives from the Agency's Office of Prevention, Pesticides and Toxic Substances; Office of Research and Development; Office of Children's Health Protection; Office of Water; and Office of Solid Waste and Emergency Response. The Task Force made many useful recommendations considered by the Office of Pesticide Programs during the development of this guidance. Comments from the public and from the FIFRA Scientific Advisory Panel also contributed to this document.

This document describes how the Office of Pesticide Programs (OPP) determines the appropriate FQPA safety factor(s) when developing aggregate risk assessments and regulatory decisions for single active and "other" (i.e., inert) ingredients of pesticide products. The guidance is specifically addressed to OPP risk assessors but also serves as an important source of information for the public and the regulated community. This guidance explains the legal framework for the FQPA safety factor and key interpretations of statutory terms (See Appendix) and describes how the FQPA safety factor provision both formalizes and expands OPP's past practice of applying uncertainty factors to account for deficiencies in the toxicological database. Because this guidance only addresses the statutory provisions of FQPA, it does not apply to any of the Agency's other regulatory programs or risk assessment processes which are carried out under different statutory authorities. As explained below, this guidance explains how OPP intends to "take into account...potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children" as directed by FFDCA section 408(b)(2)(C)(i).

A primary consideration in implementation of the FQPA safety factor provision is assessing the degree of concern regarding the potential for pre- and postnatal effects. In many cases, concerns regarding pre- and postnatal toxicity can be addressed by calculating a reference dose (RfD) or margin of exposure (MOE) from the pre- or postnatal endpoints in the offspring and when traditional uncertainty factors are applied to account for deficiencies in the toxicity data. In some instances, however, data may raise uncertainties or a high concern for infants or children which cannot be addressed in the derivation of an RfD or MOE. OPP intends to analyze the degree of concern and to assess the weight of all relevant evidence for each case. This involves examining the level of concern for sensitivity/susceptibility and assessing whether traditional uncertainty factors already incorporated into the risk assessment are adequate to protect the safety of infants and children, as well as the adequacy of the exposure assessment.

The guidance also explains how data deficiency uncertainty factors will be used to address the FQPA safety factor provision's expressed concern as to the "completeness of the data with respect to... toxicity to infants and children...." The FQPA safety factor provision regarding the completeness of the toxicity database is similar to the traditional data deficiency uncertainty factors used by the Agency to address inadequate or incomplete data. Thus, when deriving RfDs and evaluating the protection provided by FQPA safety factors, OPP intends to consider current Agency practice regarding data deficiency uncertainty factors.

Another important consideration for the FQPA safety factor is the completeness of the exposure database. Whenever appropriate data are available, OPP estimates exposure using reliable empirical data on specific pesticides. In other cases, exposure estimates may be based on models and assumptions (which in themselves are based on other reliable empirical data). This document explains how, in the absence of case specific exposure data, OPP will evaluate the safety of the exposure estimate as to infants and children and correspondingly, the appropriate FQPA safety factor.

Finally, the decision to retain the default 10X FQPA safety factor or to assign a different FQPA safety factor is informed by the conclusions presented in the risk characterization and is not determined as part of the RfD process. This guidance document describes the integrated approach used when making FQPA safety factor decisions. This is a "weight-of-evidence" approach in which all of the data, concerning both hazard and exposure, are considered together for the pesticide under evaluation. The FQPA safety factor determination includes an evaluation of the level of confidence in the hazard and exposure assessments and an explicit judgement of whether there are any residual

uncertainties identified in the risk characterization. It is at this integration stage that OPP determines how the completeness of the toxicology **and** exposure databases and the potential for pre- and postnatal toxicity were handled in the risk assessment.

ABBREVIATIONS

BMD	Benchmark Dose
CSAFs	Chemical-Specific Adjustment Factors
CSFII	USDA's Continuing Survey of Food Intakes by Individuals
DNT	Developmental Neurotoxicity (Study)
DWLOC	Drinking Water Levels of Comparison
FQPA	Food Quality Protection Act
FFDCA	Federal Food and Drug Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Ac
GLP	Good Laboratory Practice
LOAEL	Lowest-Observed-Adverse-Effect Level
MF	Modifying Factor
MOE	Margin of Exposure
NAS	National Academy of Sciences
NAWQA	National Water Quality Assessment Program
NOAEL	No-Observed-Adverse-Effect Level
OPP	Office of Pesticide Programs
PAD	Population Adjusted Dose
PDP	USDA's Pesticide Data Program
POD	Point of Departure
RfC	Reference Concentration
RfD	Reference Dose
SAR	Structure-Activity Relationship
SOP	Standard Operating Procedure
SAP	FIFRA Scientific Advisory Panel
UF	Uncertainty Factor
UF_A	Uncertainty Factor that is intended to account for the uncertainty involved in extrapolating from animal data to humans.
UF_{DB}	Uncertainty Factor that is intended to account for the absence of key data in the database for a given chemical.
UF_H	Uncertainty Factor to account for the potential variation in sensitivity among the members of the human population, including children
UF_L	Uncertainty Factor to extrapolate from the LOAEL to a (surrogate) NOAEL
UF_s	Uncertainty Factor to extrapolate from subchronic to chronic data
USGS	U.S. Geological Survey

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DETERMINATION OF THE APPROPRIATE FQPA SAFETY FACTOR(S) IN TOLERANCE ASSESSMENT

I. Introduction

On August 3, 1996, The Food Quality Protection Act (FQPA) was signed into law. 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 specifically directed EPA, in its regulatory program for setting pesticide tolerances, 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 additional default 10X factor with a different factor only if, based on reliable data, the resulting margin would be safe for infants and children [Section 408(b)(2)(C)]. The Office of Pesticide Programs (OPP) interprets this statutory provision as establishing a presumption in favor of applying an additional 10X safety factor. The Agency can depart from the presumption or default 10X approach when reliable evidence shows that a different safety factor is protective of infants and children. (See the Appendix for a complete explanation of the legal framework for the FQPA safety factor and key interpretations of statutory terms.)

This document refers to the section of the statute establishing the additional safety factor for the protection of infants and children as the **FQPA safety factor provision**. Further, this document describes both types of safety factors in the FQPA safety factor provision the default additional 10X safety factor and the "different" safety factor to be applied instead of the default value when reliable data show such different safety factor to be safe as FQPA safety factors. For the sake of clarity, OPP will refer to the statutory default 10X value as the "default" or "presumptive" 10X FQPA safety factor.

The purpose of this guidance document is to describe the policies OPP intends to apply in making determinations regarding the FQPA safety factor when developing aggregate risk assessments and regulatory decisions for single active and "other" (i.e., inert) ingredients of pesticide products. OPP has prepared a separate paper, "Consideration of the FQPA Safety Factor and Other Uncertainty Factors in Cumulative Risk Assessment of Chemicals Sharing a Common Mechanism of Toxicity," that presents the general approach attendant to making determinations regarding the traditional uncertainty factors and the FQPA safety factor for cumulative assessments (USEPA 2002). Because this guidance only addresses the statutory provisions of FQPA, it does not apply to any of the Agency's other regulatory programs or risk assessment processes that are carried out under different statutory authorities.

This guidance document has been written in light of review and comment offered by: the public during the public comment period of July to October, 1999; the FIFRA Scientific Advisory Panel (SAP) on several earlier versions over the last four years; other external parties offered in the context of these SAP meetings (USEPA 1999j); and, considering the draft reports of the Toxicology and Exposure Working Groups of the Agency 10X Task Force (see USEPA 1999c and 1999d). The Agency 10X Task Force was established in March 1998 to assist in addressing the general considerations regarding the use of the tenfold 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; Solid Waste and Emergency Response; Water; 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 Agency announced the availability of an earlier draft of this document (USEPA 1999a) and invited the public to comment in accordance with the processes suggested by the Tolerance Reassessment Advisory Committee. The document also was discussed at the May 1999 meeting of the FIFRA SAP. The guidance document has been revised, as appropriate, taking these comments into consideration. Furthermore, this guidance embodies the 1996 EPA Administrator's Directive (USEPA 1996a) and Executive Order 13045: "Protection of Children from Environmental Health Risks and Safety Risks" (EO 1997) to identify and assess environmental health risks that may disproportionately affect children. It is also noted that the draft Standard Operating Procedures (USEPA 1999b), which were also presented at the May 1999 meeting of the FIFRA SAP, will be revised to reflect this current guidance document.

This guidance document provides OPP's current thinking on application of the provision in FFDCA section 408(b)(2)(C), regarding an additional safety factor for the protection of infants and children. As such, it is intended to provide guidance to OPP risk assessors to facilitate consistent implementation by OPP of the children's safety factor provision and to increase understanding of OPP actions by regulated entities and the public. Importantly, this guidance document is a policy statement and not a legislative rule and thus is not binding on OPP or on outside parties. It does not predetermine any pesticide-specific decision regarding the children's safety factor. OPP remains free to take actions that vary from the guidance provided in the document. For example, OPP may deviate from the document based on developments in science or risk assessment methodologies or changes in policy approach. Any such action would be accompanied by an explanation for OPP's decision. Similarly, the regulated community and the public retain the right to object both to the manner in which the guidance document is applied to specific pesticides as well as to the policy considerations underlying the guidance document. Such objections could address any factual, scientific, policy, or legal conclusions or interpretations in the guidance document. If such objections are persuasive, OPP will be guided by them in the specific decision at hand and also modify the policy, as appropriate.

To facilitate consistent decision-making, OPP staff should consider this guidance document in all actions involving the additional children's safety factor. OPP staff are cautioned, however, that, because this document is a guidance policy and not a binding rule, they must consider the merit of all contentions from outside parties regarding application of the children's safety factor to specific pesticides. Should staff believe, for whatever reason, that action at variance from this guidance document should be taken, that recommendation should be flagged so that it can receive the full consideration of OPP decision-makers.

II. The Overall Approach to The FQPA Safety Factor

A. The Agency Process for Establishing a Reference Dose

Before any decisions are made on the appropriate FQPA safety factor applied to ensure the safety of infants and children from the use of a particular pesticide, all of the relevant submitted data for the pesticide should be assembled and reviewed by Agency scientists. The toxicology database is evaluated to identify potential adverse effects, to determine the adequacy of the available data to characterize potential human risks, and to analyze the relationship between dose and response, that is, the levels at which the chemical causes adverse effects in test animals. The assessment of the potential for adverse health effects in infants and children is part of the overall hazard and dose-response assessment for a chemical. Available data pertinent to children's health risks are evaluated along with data on adults and the NOAEL (no-observed-adverse-effect-level) or benchmark dose (BMD) for the most sensitive critical effect(s) based on consideration of all health effects. By doing this, protection of the health of children will be considered along with that of other sensitive populations. In most 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 involves identifying a NOAEL (or a LOAEL if a NOAEL is not available) or calculating a BMD for the sensitive critical effect (EPA 2000b). The NOAEL or BMD can be used in two ways in risk assessment: First, it can be divided by uncertainty factors and a modifying factor (MF) to account for various uncertainties in the data to derive the reference dose or RfD. The RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL (lowest-observed-adverse-affect level), or BMD, with uncertainty factors generally applied to reflect limitations of the data used. Separate RfDs may be established for different durations of exposure (e.g., acute or intermediate). Second, the NOAEL (or BMD) can be divided by the estimated human exposure 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.

EPA has been deriving chronic RfDs for oral exposures for nearly twenty years, 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 (USEPA 2001a).

EPA's longstanding RfD Process identifies five uncertainty factors and one modifying factor (sometimes described as safety factors) that may be applied to the NOAEL or BMD[1] to derive an RfD;[2] these factors are listed in Figure 1. Although the default value for each of these factors is 10X, the exact value of the uncertainty factor chosen will depend on the quality of the studies available, the extent of the database, and scientific judgment. For example, based on the weight-of-

Figure 1. Traditional Uncertainty Factors

Interspecies uncertainty factor (UF_A) which is intended to account for the uncertainty involved in extrapolating from animal data to humans.

Intraspecies uncertainty factor(UF_H) which is intended to account for the potential variation in sensitivity among the members of the human population, including children.

Uncertainty factor to extrapolate from subchronic to chronic data (UF_S), if deriving a chronic RfD.

Uncertainty factor to extrapolate from the LOAEL to a (surrogate) NOAEL (UF_L), if no appropriate NOAEL can be identified in the toxicology database.

Database uncertainty factor (UF_{DB}) which is intended to account for the absence of key data in the database for a given chemical.

Modifying factor which 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 dose

[1]The Agency has acknowledged that the historical approach to defining a NOAEL and calculating RfDs and RfCs has limitations. In response, EPA has developed draft guidance on an alternative method the BMD Approach (USEPA 2000b). The BMD is defined as the statistical lower confidence limit on the dose (BMDL) producing a predetermined level of change in response compared with the background response. A BMD is derived by fitting a mathematical model to the dose-response data. The Agency is still gaining experience with BMD analyses and has not yet formally finalized standard operating procedures. It is proposed Agency guidance to use the BMDL for single chemical assessment.

[2]Guidance for calculating reference concentrations (RfCs) for risk associated with inhalation exposure can be found in USEPA 1994.

evidence[3], often a value of 3X is used to address database deficiencies for pesticides, given the large amount of data typically available. Agency policy is that risk assessors should not derive an RfD if five or more uncertainty/modifying factors would be judged necessary; the uncertainty would simply be too great in such situations to derive a quantitative value. EPA has convened a technical panel of the Agency's senior scientists, called the RfD Technical Panel, to evaluate the current RfD and RfC process, in particular, with respect to how well children and other potentially sensitive subpopulations are protected. This panel produced a draft report in August 2001 entitled, "Review of the Reference Dose And Reference Concentration Processes"[4]. Several recommendations were made in this report concerning the RfD process including the use of the modifying factor. The RfD Technical Panel considers the purpose of the modifying factor to be sufficiently subsumed in the general database UF and recommends the discontinuation in the use of the MF. The approach to using chemical-specific data for toxicokinetic and toxicodynamic components of UFs has been discussed in the reference concentration methodology for estimating inhalation risk (EPA 1994). The Technical Panel encourages the Agency to develop its own guidance for chemical-specific adjustment factors (CSAFs) based on some of the available methodologies (e.g., International Programme on Chemical Safety).

B. The Relationship Between FQPA Safety Factors and Traditional Uncertainty Factors

OPP interprets the FQPA safety factor provision as dictating that the FQPA safety factor is to be applied in addition to the two baseline uncertainty factors that account for: (1) potential differences in sensitivity and variability among humans, i.e., the "intraspecies" uncertainty factor (UF_H); and (2) potential differences in sensitivity between experimental animals and humans, if animal data have been used as the basis for deriving the hazard values, i.e., the "interspecies" uncertainty factor (UF_A). Further, as explained below, OPP believes that the FQPA

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[3]A weight-of-evidence evaluation requires a critical analysis of the entire body of available data for consistency and biological plausibility. Potentially relevant studies should be judged for quality, and studies of high quality given much more weight than those of lower quality. Where both epidemiological and experimental data are available, similarity of effects between humans and animals is given more weight. If the mechanism or mode of action is well characterized, this information is used in the interpretation of observed effects in either human or animal studies. "Weight-of-evidence" is not to be interpreted as simply tallying the number of positive and negative studies.

[4]The August 2001 draft report, *Review of the Reference Dose And Reference Concentration Processes* (USEPA 2001d), developed by the Agency's RfD technical panel is in the process of being finalized.

safety factor both incorporates prior Agency practice on additional safety factors and expands such prior practice as well. (See Appendix for further details.) Any reference in this document to an "additional" FQPA safety factor is simply meant to convey that the FQPA factor is in addition the intra- and interspecies uncertainty factors. Generally, this document does not repeat the term "additional" throughout on the assumption that the reader will understand that FQPA safety factors are additional to the standard, baseline uncertainty factors for intra- and interspecies.

One of the statutory reasons for the presumptive FQPA safety factor is to account for data deficiencies that raise concern for infants and children. In the past, OPP has followed the Agency's risk assessment policies and practices and has applied additional factors to account for toxicological data deficiencies even prior to the passage of FQPA. Both the observed adverse effects shown in studies and the completeness of the toxicology database have been considered when determining the appropriate composite uncertainty factor needed to calculate the RfD. Considering this, it is OPP's view that FQPA **codifies**, to a large extent, the Agency's pre-FQPA use of uncertainty factors in addition to the standard inter- and intraspecies factors. It should be noted that the traditional Agency RfD process has evolved since passage of the FQPA to include more conscious focus on whether the RfD is protective of infants and children. This has closed the gap between the traditional RfD process with its use of uncertainty factors to address data deficiencies and the approach embodied in the FQPA safety factor provision.

In addition, by specifically including a reference to potential pre- and postnatal toxicity as one of the factors justifying an additional 10X factor for pesticides, Congress effectively **expanded** OPP's pre-FQPA practice concerning the role that substantive study results play in safety factor determinations by placing increased emphasis on potential pre- and postnatal toxicity. Another expansion of pre-FQPA practice was affected by Congressional reference to the completeness of the exposure database which places 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.

C. OPP's General Approach to FQPA Safety Factor Decisions

Under the FQPA safety factor provision, EPA must apply the default 10X safety factor unless EPA concludes, based on reliable data, that a different safety factor would protect the safety of infants and children. Risk assessors, therefore, should presume that the default 10X safety factor applies and should only recommend a different factor, based on an individualized assessment, when reliable data show that such a different factor is safe for infants and children. Nonetheless, OPP believes that it is critical to the protection of infants and children that it does not rely on a default value or presumption in making decisions under Section 408 where reliable data are available that support an individualized determination (Refer to Appendix).

Incomplete toxicology databases are not equally incomplete. Even with a complete toxicology database, all pre- or postnatal toxicities are not of equal concern. Consider these simple examples:

> A pesticide with weaknesses in its toxicology and/or exposure databases but in which the existing data are adequate to assess potential pre- or postnatal toxicity and indicate no concern;
>
> A pesticide with a complete database that demonstrates that it does result in pre- or postnatal toxicity; and
>
> A pesticide with an incomplete database that, nonetheless, shows the potential for pre- and postnatal toxicity.

If the 10X factor is applied as a default in all of these circumstances, each of these pesticides would get exactly the same treatment, which could result in underprotecting in one case but not in another.

For these reasons, rather than relying on the 10X default value OPP makes specific case-by-case determinations as to the need and the size of the additional factor if reliable data permit. Determination of the magnitude of the overall safety factor or margin of safety involves evaluating the completeness of the toxicology and exposure databases and the potential for pre- or postnatal toxicity. Individualized assessments may result in the use of additional factors greater or less than, or equal to 10X, or no additional factor at all.

Given the extensive amount of data available, OPP believes that in most instances there will be sufficient reliable data to conduct an individualized assessment of what additional FQPA safety factor is necessary to assure the safety of infants and children taking into account potential pre- and postnatal toxicity and the completeness of the toxicity and exposure databases. Accordingly, this guidance document focuses primarily on the considerations relevant to determining a safety factor "different" from the default 10X that protects the safety of infants and children. Discussions in this document of the appropriateness, adequacy, need for, or size of an additional safety factor are premised on the fact that reliable data exist for choosing a "different" factor than the 10X default value.

D. Safety Factor Decisions Under FQPA versus Uncertainty Factor Decisions in Agency RfD Determinations

From an Agency-wide perspective, it is very important to distinguish those factors introduced as a result of FQPA from traditional uncertainty factor practice. OPP risk assessments are frequently relied upon by other offices within EPA; such other offices are not governed by Section 408 of FFDCA. Thus, for OPP risk assessments to be usable by other portions of the Agency, it is critical that OPP define, if possible, which aspects of a safety factor are unique to FQPA and which follow the traditional Agency RfD process. At the same time, it is important to recognize that the FQPA safety factor, as defined in FQPA, does not stand wholly apart from traditional agency practice but rather incorporates that practice as a part of the safety factor. Thus, there is a large degree of overlap between the FQPA safety factor and traditional agency practice as to the use of uncertainty factors to account for incomplete characterization of a chemical’s toxicity.

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

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

Traditional uncertainty factors which are those used prior to FQPA passage to account for database deficiencies and are now codified by the FQPA; and

Special FQPA safety factors which are those used to apply to the aspect of a "different" FQPA factor that is unique to FQPA and which are introduced primarily as a result of FQPA.

Any given FQPA safety factor may be comprised of these two components. By adopting this terminology EPA hopes that its safety factor determinations will be transparent. Other important terminology to remember includes: (1) "Presumptive" or "default" FQPA factor refers to the FQPA additional 10X safety factor mandated by the statute unless it is decided that there are reliable data to choose a different factor; and (2) "additional" FQPA factor is used to mean that all FQPA factors (including traditional uncertainty and special FQPA factors) are in addition to the inter- and intraspecies uncertainty factors.

As Figure 2 illustrates, the "traditional uncertainty factors" are those used (as appropriate) in the derivation of the RfD for a particular pesticide (Refer to Figure 1 for a description of the factors). Within the traditional uncertainty factor category, there are several factors that are generally used to account for deficiencies in the toxicity database (see Section III), building on existing Agency practice regarding the application of a traditional database uncertainty factor.

Figure 2. Traditional Uncertainty Factors That Can Be Used in RfD Derivation

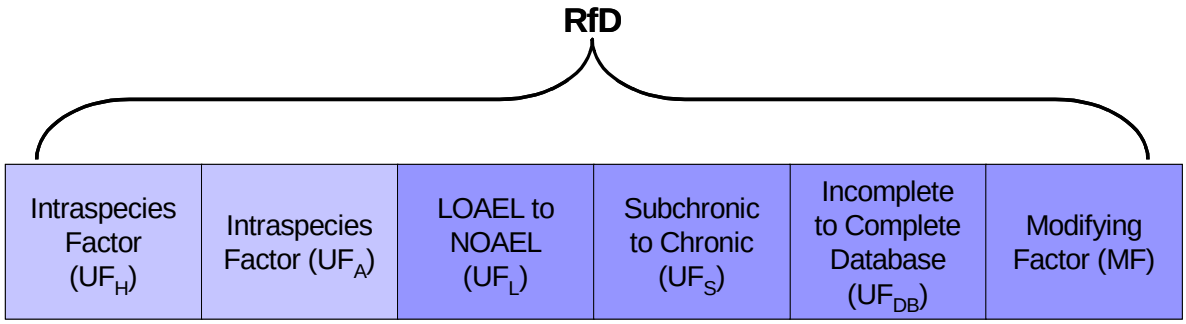


Figure 3 illustrates the relationship between the RfD and the Population Adjusted Dose (PAD) for a particular pesticide. The PAD is simply the RfD divided by any special FQPA safety factor(s) employed for the protection of infants and children. OPP considers the special FQPA factor to be an expansion of traditional Agency RfD practice. Special FQPA safety factors are intended to account for:

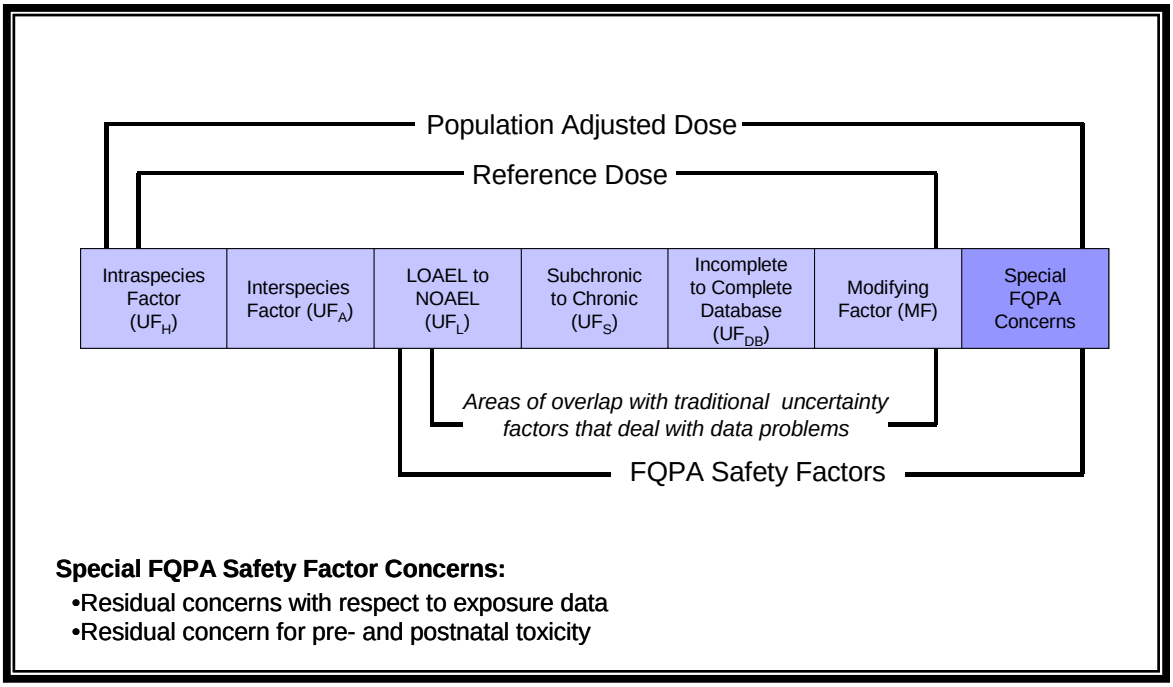
Residual concerns for susceptibility given the available evidence on pre- and postnatal toxicity (see Section IV); and/or

Residual concerns or uncertainties in the exposure assessment (see Section V).

It should be noted that in the evaluation of pre- and postnatal toxicity, the risk assessor should make case-by-case decisions using criteria for judging the potential and degree of concern of a particular pesticide to produce pre- and postnatal effects (described in Section IV; also see USEPA 1999c). While some of the concerns regarding pre- and postnatal toxicity may be addressed when an RfD or MOE is based on the pre- or postnatal endpoints in the offspring, this may not be adequate when faced with data that suggest a high degree of concern. To the extent that these greater concerns regarding pre- and postnatal toxicity cannot be addressed in the derivation of an RfD or MOE, the residual concerns or uncertainties may be addressed by the use of a special FQPA safety factor in the final stage of the risk assessment process.

Figure 3 also is combined with Figure 2 to show the relationship between the traditional uncertainty factors which were used prior to FQPA passage to account for database deficiencies (and are now codified by FQPA) and the special FQPA safety factor concerns which were introduced primarily as a result of the FQPA.

Figure 3. Relationship between RfD Derivation and the PAD Calculation



E. Stages in the FQPA Safety Factor Decision-Making Process

Available data pertinent to children's health risks are evaluated for a particular pesticide at three different stages in the OPP risk assessment process. Decisions regarding the FQPA safety factor are informed by the conclusions presented in the risk characterization.

Hazard and Dose-Response Assessment. During this stage of the OPP risk assessment process, the toxicology data are considered, hazards identified, and appropriate endpoints are selected for estimating risk associated with various exposure scenarios (dietary and nondietary). Toxicity data gaps are identified and the significance of the data deficiency is evaluated. The RfD is calculated taking into account all the data and any uncertainties in the database. A degree of concern analysis is also conducted for any pre- or postnatal toxicity identified in the available data to inform the risk characterization regarding decisions on the special FQPA safety factor.

Exposure Assessment. During this stage, decisions are made regarding deficiencies in the exposure databases (food, water, and residential) and/or in the methodologies used to estimate each exposure scenario and the extent to which these can be accounted for in the assessment.

Risk Characterization. It is at this stage of the OPP risk assessment process that the data on toxicity and exposure are integrated and a decision is made whether there are residual concerns regarding the adequacy of the risk assessment (including both the hazard and exposure assessments) and, based on the weight of all evidence, whether the concerns related to the presumptive FQPA 10X safety factor have been accounted for. If OPP finds that reliable evidence support a different factor a decision about the size of that factor is also be made at this stage.

It is important that, at each stage of the OPP risk assessment process, the risk assessors clearly document the decisions and reasons for choosing to use a particular uncertainty, modifying, or safety factor and the level of confidence in the resulting assessment. Once decisions regarding whether reliable data exist to set a different FQPA safety factor (and, if appropriate the magnitude of any such factor) are made, the final decision on the FQPA safety factor is based on the integration of results from the hazard and exposure assessments considering: the nature and level of confidence in these assessments; the degree of concern for potential toxicity to the fetus, infants, and children; and any residual uncertainties that are not otherwise taken into account.

F. The Population Adjusted Dose

As seen in the previous section (Figure 3), the PAD is a modification of the RfD used by OPP to accommodate any special FQPA safety factor applied to address the potential for pre- and postnatal toxicity and the completeness of the exposure databases. The PAD is equal to the established RfD divided by any special FQPA safety factor (see Section VI.B). When no special FQPA safety factor is retained (i.e., 1X), the RfD is identical to the PAD. In situations where EPA decides to retain the default FQPA 10X safety factor, the value resulting would be called a PAD. It should also be noted that because separate FQPA safety factor decisions may be necessary for different population subgroups and different durations of exposure, the calculated PAD may be scenario-specific.

III. Toxicity Considerations Related to Data Completeness and the Assessment of Risk to Infants and Children

This section describes the general approaches used in a weight-of-evidence evaluation of the "completeness of data with respect to...the toxicity to infants and children" that should be considered when evaluating whether reliable data are available to support a FQPA safety factor different from the default 10X FQPA safety factor and what level of "different" FQPA safety factor would be safe for infants and children.

An important aspect of hazard assessment and characterization is to determine whether there is sufficient information to evaluate potential adverse effects in humans posed by a given chemical. When toxicology information is deficient, due to the absence of needed data or the limitations of existing data, and potential risks cannot be characterized with confidence, the Agency has traditionally used one or more uncertainty factors to insure that risk assessments are protective of human health. These uncertainty factors are intended to account for the potential for deriving an underprotective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. Examples of such uncertainty factors include: a factor to account for estimating a NOAEL from a LOAEL (UF_L), a factor for estimating chronic effects from a subchronic study (UF_S), and a factor to further reduce the RfD because of missing toxicity data that may show effects at lower doses (UF_{DB}). An uncertainty factor used to account for the absence of toxicology data has traditionally been referred to as the database uncertainty factor (UF_{DB}). In this document, OPP refers to all of the toxicology data-related uncertainty factors as "data deficiency uncertainty factors" (i.e., UF_S, UF_L, UF_{DB} See Figure 1).

As explained above, the FQPA safety factor incorporates EPA's traditional practice regarding use of factors (i.e., UF_S, UF_L, UF_{DB}) to address uncertainties in the toxicology database. Accordingly, the Agency's traditional practice regarding uncertainty factors is an important reference point for assessing what level of safety factor is needed to protect infants and children when there is insufficient or inadequate toxicity data. This prior Agency practice, however, must be viewed in light of the mandates of the FQPA. The Agency's pre-1996 practice regarding use of the database uncertainty factor (UF_{DB}) tended to focus on a somewhat narrow group of studies. Given FQPA's emphasis on the protection of infants and children, the risk assessor should use, in decisions involving the FQPA safety standard, the database uncertainty factor to address data deficiencies bearing on risks to sensitive subpopulations, including infants and children. In this way, the risk assessor

will insure that use of a database uncertainty factor will address FQPA concerns with regard to the completeness of the database.

The broad use of the database uncertainty factor under FQPA to respond to potentially relevant database deficiencies is characteristic of how general Agency practice concerning the database uncertainty factor in other contexts has evolved since the passage of FQPA. The Agency RfD/RfC Technical Panel recently evaluated the existing methodologies for the derivation of a chronic RfD or RfC and also proposed principles to guide the Agency in developing RfDs and RfCs for less-than-lifetime durations of exposure (e.g., acute, short-term and longer-term) (EPA 2001b). The RfD/RfC Technical Panel noted in its draft report that (USEPA 2001d):

> [t]he Technical Panel agrees with the Toxicology Working Group of the 10X Task Force (USEPA 1999c) that an additional default child-specific factor beyond the interspecies, intraspecies, and database deficiency uncertainty factors is not necessary, *if* appropriate care has been taken in accounting for *all* deficiencies and uncertainties in the database using the currently available uncertainty/variability factors. [emphasis added]

Moreover, it is clear from recent assessments that the Agency is looking beyond the standard datasets traditionally used to derive high confidence RfDs/RfDs in evaluating children's health risks and risks to other sensitive subpopulations.

The commonalities in the Agency's existing practice regarding the database uncertainty factor and OPP's use of the factor to address FQPA concerns will help insure consistency in Agency risk assessments. Specifically, it should insure that the RfDs produced by OPP and other EPA program offices should usually be the same for the same chemical.

Described below is guidance on the evaluation of the "completeness of the toxicology database" regarding potential health risks to children and the approach to evaluate the need for an uncertainty factor to address gaps or inadequacies in the available toxicity database. Particular attention is focused on the need for the database uncertainty factor (i.e., the uncertainty factor pertaining to missing data that doesn't allow complete characterization of toxicity). The guidance outlined in this section draws on both the recommendations of the Agency's 10X Task Force Toxicology Working Group April 1999 draft report "Toxicology Data Requirements For Assessing Risks of Pesticide Exposure to Children's Health" (USEPA 1999c), as well as the recent recommendations of the Agency's Risk Assessment Forum (RAF) RfD/RfC Technical Panel August 2001 draft report (USEPA 2001d). The purpose of the RfD/RfC Technical Panel was to: evaluate the current RfD/RfC process, in particular, with respect to how well children and other potentially sensitive subpopulations are protected; consider new scientific issues that have become important and of greater concern in risk assessment; and raise issues that should be explored or developed further for application in the RfD/RfC process.

A. "Completeness of the Toxicology Database" For Assessing Risk of Pesticide Exposure to Children's Health

EPA has regulated pesticides for over thirty years and throughout this time, the Agency has attempted to tailor its data requirements for assessing the potential risks of particular pesticides to the characteristics and use patterns of the individual pesticide. Although OPP determines the data required for a specific pesticide product on a case-by-case basis, the starting point for all pesticide products is EPA's toxicology data requirements described in 40 CFR Part 158 (available at: http://www.access.gpo.gov/nara/cfr/index.html. The regulations specify the types of studies in ten different scientific disciplines including toxicology, environmental fate, and residue chemistry, among others required to support the registration (or reregistration) of a conventional pesticide product. In addition, the regulations reference appropriate "test guidelines" that contain descriptions of the methodology that sponsors should use to conduct the required studies (available at: http://www.epa.gov/OPPTS_Harmonized/). Additionally, the regulations make clear that in order to have sufficient information to assess the hazard potential of a chemical, OPP may impose additional data requirements or, if conducting a particular study would not be necessary to evaluate the potential risks of a pesticide, OPP may waive the data requirement.

OPP typically receives a variety of studies based on pesticide treatment of adults, pregnant females, and young animals. Some of these studies are routinely required and some are conditionally triggered. Routinely required studies for conventional food use pesticides[5] include for example, subchronic (90-day) feeding studies in rodent and nonrodent species, chronic feeding studies in rodent and nonrodent species, carcinogenicity studies in two rodent species, prenatal developmental toxicity studies in rodents and nonrodents, and a two-generation reproduction study in rodents. Current "conditionally triggered" studies for example, dermal penetration, 21-day dermal, subchronic dermal, subchronic inhalation, acute and subchronic neurotoxicity studies in rodents, acute and subchronic delayed neurotoxicity in hens, a developmental neurotoxicity (DNT) study in rodents are triggered by some special characteristic of the pesticide (e.g., its chemical class) or by potential use and exposure patterns (e.g., residential uses) or by the results of

[5]Other classes of food-use pesticides (both actives and inert ingredients) require fewer toxicity studies. Although this guidance does not specifically address how to evaluate the completeness of the toxicity database for these chemicals, the risk assessor should apply the same broad principles described here when making decisions about the FQPA safety factor for such pesticides.

routinely required studies. Further, as noted, OPP has the authority to impose data requirements on pesticides beyond those contained in 40 CFR 158. Therefore, OPP is able to require data beyond those routinely or conditionally required on an individual pesticide that it determines are needed to adequately characterize the hazard potential of the pesticide, including potential hazards to infants and children.

All of these studies, whether routinely or conditionally required or required due to the special characteristics of a pesticide or group of pesticides, potentially bear on the risks posed to infants and children. Accordingly, the "completeness" inquiry should be a broad one that takes into account all data deficiencies. In other words, the risk assessor should consider the need for traditional uncertainty factors not only when there are inadequacies or gaps in currently required studies on pesticides, but also when other important data needed to evaluate potential risks to children are missing or are inadequate.

OPP recognizes the need to improve and revise its data requirements for pesticides. Since the promulgation of FQPA, a number of activities have been ongoing within and outside the Agency to evaluate the types of testing approaches that would provide more efficient and thorough evaluation of potential human risks, including children's risks. These include: consideration of the need for new studies as well as the need to modify existing guideline studies to provide a more comprehensive coverage of life stages; a more systematic evaluation of toxicokinetics; and a more focused evaluation of structural and functional toxicity in the young. For example, OPP plans to publish proposed revisions to its pesticide data requirements regulation, 40 CFR 158, and expects to ask for comment on a requirement for DNT testing, which utilizes information about each chemical and its toxicity to develop a rational, science-based approach to the study design and testing strategy. OPP further acknowledges that the scientific community is developing, or in some cases already utilizes, other studies for evaluating the young which are not required studies and for which there are no formal, standardized test guidelines. There are ongoing activities within OPP and the Agency to consider the need for other guidelines or studies important to evaluate risk in infants and children, such as toxicokinetics in fetuses and/or young animals, direct dosing of the offspring prior to weaning, enhanced DNT studies including specialized testing of sensory and/or cognitive function, developmental immunotoxicity, and enhanced evaluations of the potential to induce effects related to endocrine disruption. These areas represent possible future revisions to current guidelines or possible development and implementation of new guidelines.

B. Use of an Uncertainty Factor to Address Deficiencies in the Available Toxicity Database

The risk assessor should take into account the Agency's practice and policy on the use of traditional uncertainty factors in considering the significance of any "data gap" needed for hazard characterization. With regard to data gaps and the database uncertainty factor, the Agency has traditionally considered a group of five studies to be the minimum for deriving a "high confidence" chronic RfD for dietary exposure (available at: http://www.epa.gov/iriswebp/iris/index.html (USEPA 2001a) or Dourson et al. 1996).[6] These toxicity studies include: two chronic oral studies in different species, two prenatal developmental studies in different species, and a multigeneration reproductive toxicity study in rats. The risk assessor should continue to build on this Agency policy regarding which data are most important for a "high confidence" RfD for chronic oral exposure. The absence of any of these studies suggests that the existing data are not sufficient to address and relieve uncertainties regarding the hazards of the chemical and would typically give rise to the need for a database uncertainty factor to protect the safety of infants and children.

In addition to considering any data gaps involving these five studies, the risk assessor should as is now standard Agency practice evaluate other data gaps, particularly those that pertain to evaluating risk to children and other sensitive subpopulations. When data gaps exist, the risk assessor should consider the general, overall value of the particular type of study to the risk assessment. Information about the potential adverse effects of a chemical substance should take into consideration all relevant data, as well as generally how likely those effects are to be the most sensitive toxic endpoint on which the RfD or other hazard value is based. The analysis of data gaps should evaluate the overall value of the missing study to the risk assessment process, including characterization of effects on the young. In deciding to apply a database uncertainty factor to account for missing studies, the risk assessor should evaluate how thorough the testing is with respect to life stage assessment, endpoint assessment, and duration of exposure. It should be emphasized that studies using adult animals may help inform the judgment about potential effects in the young and the need for additional studies. At a minimum, the

[6]OPP scientists evaluate the acceptability of data from a study based in part on whether the study was conducted in accordance with the Agency's test guidelines and Good Laboratory Practice (GLP) regulations at 40 CFR 160. The test guidelines and GLP regulations 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, and whether available data raise concerns for toxicities that have not been adequately characterized.

analysis should consider but need not be limited to:

Toxicity data available on the particular chemical;

Toxicokinetic and mode of action information;

Potential for adverse effects shown by the available data;

Type and number of missing studies; and

Available information on the toxicity of structurally-similar chemicals.

If there are data from the available toxicology studies that raise suspicions of developmental toxicity and signal the need for other types of testing, e.g., DNT studies, developmental immunotoxicity studies, developmental carcinogenesis studies, or developmental endocrine toxicity studies, then the database uncertainty factor should be considered as a means of taking into account the absence of these data. Also in determining the need for a database uncertainty factor, the risk assessor should evaluate how likely the absence of a particular study will affect the point of departure (POD) for the RfD/RfC (by identifying new effects or effects at lower levels) that could significantly change the outcome of the overall risk assessment, or alter, in other ways, the registration status of a chemical.

In determining the size of any uncertainty factor, the risk assessor should consider the quality of the studies available, the extent of the database, and how much impact the missing or inadequate data may have on determining the toxicity of a chemical. Scientific judgment should be used in determining the appropriate size of the uncertainty factors to apply based on the toxicology data set available for the pesticide and based on the understanding of whether the missing or inadequate data on a pesticide are more (or less) likely to provide information that will better characterize the potential toxicity. The relative weight given to the absence of a study or inadequacies in an existing study will, thus, depend on the scientific understanding of a particular kind of data and the understanding of the hazard potential for the pesticide.

This guidance recommends that in assessing the significance of any inadequacies in the study or the absence of the study, the risk assessor be advised by overall patterns of experience with the study. The risk assessor should make the decision regarding the size of the database uncertainty factor on a case-by-case basis considering which studies are missing and how many studies are missing. Data deficiencies are often addressed with a 3X, depending on the weight-of-evidence, when deriving RfDs. However, if missing data are considered to be critical to understanding the potency of a chemical and have a good possibility of revealing an especially sensitive subgroup, the size of the uncertainty factor likely would be 10X. There may be situations where a factor greater than 10X is justified based on the data missing and a considerable amount of uncertainty in the weight-of-evidence evaluation. The risk assessor should consider the degree of uncertainty associated with the missing data and how additional information would improve the understanding of the pesticide's potential risks, i.e., whether the data are expected to reduce some of the residual uncertainty in the risk assessment. If adequate data to characterize potential hazard to infants and children are available, then there would be reliable data with respect to the completeness of the toxicity database to support establishing a different FQPA safety factor.

Therefore, a determination of the possible need for and size of the database uncertainty factor will necessarily involve an assessment that considers the overall weight-of-evidence to evaluate the significance of the data deficiency. When additional data are required, consideration of the factor would generally occur only when a study is being required "for cause," that is, if a significant concern is raised based upon a review of existing information, not simply because a data requirement has been levied to expand OPP's general knowledge.

C. Factors for Weighing the Potential for Other Types of Developmental Toxicity

The DNT study is the only guideline study currently available that evaluates potential functional effects other than reproductive function in young animals. Other types of studies are being considered for guideline development as noted previously in this section (e.g., developmental immunotoxicity). These types of studies may be very useful and relevant to the consideration of the potential hazard to infants and children. Although general guidance is given above in Section III.B for making weight-of-evidence decisions regarding the application of the database uncertainty factor to account for the absence of any study, the absence of a DNT is used here as an example of a weight-of-evidence approach for consideration of the traditional database uncertainty factor.

A number of factors, as shown in Figure 4, should be taken into account when making judgements about the need for a traditional database uncertainty factor in the absence of a DNT study for a given pesticide. Similar types of factors may be considered for evaluating other types of developmental toxicity that may be needed to adequately characterize the toxicity potential for infants and children. It should be emphasized that although the factors listed in Figure 4 are considered to be comprehensive, they do not necessarily represent an inclusive description of all lines of evidence that should be considered. The decision regarding the need for a database uncertainty factor to address the absence of a DNT or other types of developmental toxicity studies should be based on weighing all lines of evidence (such as those factors described in Figure 4) for the chemical of interest, and combining the entire body of evidence to make an informed judgment on the need for, and size of, the factor. Judgement about the weight-of-evidence involves:

considerations of the quality and adequacy of available data;

consistency of responses;

the multiplicity of observations in independent studies; and

the severity, potency, persistence and latency of effects induced by the agent in question.

Additional information bearing on the degree of concern about a pesticide’s potential for DNT may also be gained from:

comparative pharmacokinetic and metabolism studies;

structure-activity relationship (SAR) analysis; and

other studies of an agent's physical and chemical properties.

As emphasized above, the factors in Figure 4 should not be scored mechanically by adding pluses and minuses; rather, they should be judged in combination. Simply because OPP has required a DNT for a particular pesticide does not necessarily mean that a database uncertainty factor is needed. However, if the available information indicates that a DNT study is likely to identify a new hazard or effects at lower dose levels of the pesticide that could significantly change the outcome of its overall risk assessment, the database uncertainty factor should be considered.

Figure 4. Factors to Consider When Characterizing the Degree of Concern for the Absence of a DNT Study

The substance and/or metabolite/degradation product demonstrates a potential to:

Cause treatment-related neurological effects in adult animal studies, such as:
- Clinical signs of neurotoxicity
- Neuropathology
- Functional or behavioral effects

Cause treatment-related neurological effects in developing animals, following pre- and/or postnatal exposure, such as:
- Nervous system malformations or neuropathology
- Brain weight effects in offspring
- Functional or behavioral changes in the offspring

Elicit a causative association between exposure and adverse neurological effects in humans in epidemiological studies

Evoke a mechanism that is associated with adverse effects on the development of the nervous system, such as:
- SAR relationship to known neurotoxicants
- Altered neuroreceptor or neurotransmitter responses
- Altered hormonal responses

IV. Toxicity Considerations Related to The Degree of Concern For Potential Pre- And Postnatal Effects on Infants And Children

This section describes the general approaches used in a weight-of-evidence evaluation of the "potential pre- and postnatal toxicity" that should be considered when evaluating whether reliable data are available to support an FQPA safety factor different from the default 10X FQPA safety factor and what level of "different" FQPA safety factor would be safe for infants and children. As part of the toxicological considerations, OPP evaluates potential pre- and postnatal toxicity on a case-by-case basis taking into account all pertinent information. If toxicity data indicate no concern for pre- and postnatal toxicity, then the risk assessor should treat the presumption for use of the default 10X safety factor as having been obviated with respect to the potential for pre- and postnatal toxicity. If toxicity data indicate pre- and postnatal toxicity, the risk assessor should assess the level of concern for such effects taking into account several factors or lines of evidence including the degree to which protection for infants and children is provided by the standard approach for deriving RfDs through the application of traditional uncertainty factors. In particular, the risk assessor should consider the protection accorded infants and children by the intraspecies uncertainty factor. The intraspecies uncertainty factor is applied to account for potential 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 1999 report of the 10X Toxicology Working Group (USEPA 1999c). On the whole, OPP interprets these evaluations along with statements in the 1993 National Academy of Sciences (NAS) Report (NRC 1993) as meaning that for most chemicals the very large majority of people, including children, respond sufficiently similarly so that the tenfold intraspecies uncertainty factor is adequate to cover any variability that may exist in the human population. At the same time, there are chemicals for which some humans may display a greater range of variability and sometimes that variability appears age-related, with children exhibiting a greater degree of sensitivity than adults. The adequacy of the standard intraspecies factor to address the potential for greater sensitivity or susceptibility of children should be considered in the context of evidence on potential pre- and postnatal toxicity as discussed below.

If the assessment of the level of concern for pre- or postnatal toxicity does not indicate a high level of concern, the risk assessor should consider the presumption for application of the default additional 10X safety factor to be obviated with respect to the potential for pre- and postnatal toxicity. If not if the level of concern is high the risk assessor should recommend the use of the default additional 10X safety factor unless reliable data exist to account for and describe the level of uncertainty regarding the potential for pre- or postnatal toxicity. If such uncertainty can be addressed by reliable data, the risk assessor should recommend use of a different FQPA safety factor (referred to in this document as a special FQPA factor) to protect the safety of infants and children.

As discussed in detail below, the risk assessor should not assume that there is a high level of concern for pre- or postnatal toxicity based solely on an apparent difference in sensitivity or susceptibility of the young. Further, the risk assessor should keep in mind that before making a decision about the need for a special FQPA safety factor, the following should be considered: the overall uncertainties in the hazard and exposure assessments; the completeness of the data; the traditional uncertainty factors applied to the NOAEL (or BMD); and other factors applied in the dose-response assessment.

A. Determining Degree of Concern for Pre- and Postnatal Toxicity

An evaluation of data relevant to the potential pre- or postnatal toxicity of a pesticide allows for determination of whether the young may be more sensitive or susceptible following exposure. In general terms, there is increased susceptibility or sensitivity when data demonstrate unique effects (e.g., a different pattern of effects of concern) or adverse effects in the young that are of a type similar to those seen in adults, but occur either at doses lower than those causing effects in adults, occur more quickly, or occur with greater severity or duration than in adults.

Once it has been established that data show pre- or postnatal toxicity, then a determination of the degree of concern for those effects needs to be made. The situations that would raise or lower a concern for the young cannot be simply encapsulated. Key lines of evidence or factors that would raise or lower concern are illustrated in Table 1. The factors listed in Table 1 generally follow the recommendations of the Toxicology Working Group of the Agency’s 10X Task Force. It should be emphasized that Table 1 is for illustrative purposes and should not be interpreted as all inclusive. Furthermore, the factors listed in Table 1 are considered in a weight-of-evidence approach for making judgments about the degree of concern for potential

pre- and postnatal toxicity in humans in the context of the entire toxicity database. No single factor presented in Table 1 determines the overall level of concern for the young. An integrative approach is important because, for example, positive animal findings may be diminished by other key data (e.g., toxicokinetic or mechanism of toxicity information), or likewise, a weak association found in epidemiological studies may be bolstered by experimental findings in animal studies. As in any weight-of-evidence approach, it is important to consider the quality and adequacy of the data, and the consistency of responses induced by the chemical across different studies.

Table 1. Factors for Evaluating Degree of Concern for Pre- and Postnatal Toxicity from Human and/or Animal Data Sets: A Weight-of-Evidence Approach

Factor	Degree of Concern	
	Increasing Weight (i.e., higher degree of concern)	Decreasing Weight (i.e., lower degree of concern)
Pre- and Postnatal Toxicity	Effects found in humans related to exposure Same types of effects seen in more than one species Effects of a different type with greater potential consequences in young compared to adults Persistence or relatively longer recovery of effects in young compared to adults	No adverse human and/or animal effects associated with exposure Similar response in young with relatively shorter recovery compared to adults
Dose-Response	Effects observed at a lower dose in young compared to adults NOAEL not identified Poor data on dose-response	Effects at higher dose level in young compared to adults, or only at high doses in the presence of severe generalized toxicity Good data on dose-response that allows for confident identification of NOAEL or BMD
Toxicokinetics	Metabolic profile indicates higher internal dose of active moiety in young compared to adult, or in humans compared to animals	Metabolic profile indicates lower internal dose of active moiety in young compared to adults, or in humans compared to animals
Mode of Action	Mode of action supports relevance to humans and concern for animal findings Mode of action may lead to several adverse consequences in the offspring	Evidence indicates that mode of action is species-specific, and thus not relevant to humans Evidence indicates that humans are less sensitive than the animal model

The potential for pre- and postnatal toxicity can be determined from human and animal studies. Although human studies are seldom available, human data are the most relevant data for assessing potential health risks. When sufficient human data are available to judge that an adverse developmental outcome is related to exposure, the degree of concern increases. When sufficient human evidence is available to judge that exposure to a pesticide does not cause pre- or postnatal toxicity, there would be a very low degree of concern. However, sufficient human evidence to show that there are no effects is very difficult to obtain because more data and evaluation of a wide range of endpoints is necessary. Animal studies can provide evidence of a potential association between exposure and effect in humans. Thus, in the absence of human evidence, a consistent response across several different laboratory species would raise concern for the potential for effects in humans, for example. The factors for judging sufficiency of human and animal data are discussed in the EPA's 1991 developmental toxicity and 1996 reproductive toxicity risk assessment guidelines (USEPA 1991a; USEPA 1996b).

As illustrated in Table 1, when evaluating relevant data, it is important to consider the biological responses observed, such as whether the effects in young animals are of a different or similar type, last longer, or are more severe compared to adults. This comparison should be based on an evaluation of all pertinent studies, although it is ideal to have companion adult data from the same studies as those in developing animals. When comparing developmental data to adult data, it is important to keep in mind that: (1) when exposure occurs during early embryonic development and/or critical stages of organogenesis, 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 have sufficiently developed to be functional but not fully mature, the toxic outcomes that result are likely to resemble those experienced by an adult but the degree of response may be different or the adverse effect may be expressed sooner compared to the adult. For example, exposure to a chemical during organogenesis may result in abnormal development of the genital tract such that the offspring cannot reproduce, while exposure to the same chemical in the adult may result in liver toxicity. Both outcomes are adverse, but the nature and consequences for the offspring are very different from the adult. Although a different pattern of effects in the young compared to adults may raise concern, it is important to consider other factors concerning the observed response, such as, progression, severity, recovery time or persistence, and dose-response (discussed below). For example, there would be greater concern for effects that were irreversible and of a greater potential consequence to the young compared to observed effects in adults that are of a transient and minimal nature, even when they occur at the same dose.

B. Degree of Concern with Respect to Dose-Response

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 does and does not cause adverse effects in test animals. The degree of concern could decrease when adverse effects are seen only at dose levels higher or similar to those causing effects in adults. The degree of concern could also decrease when developmental or adverse effects are seen only at higher doses (e.g., approaching or greater than the maximum tolerated dose), or observed only in the presence of severe or generalized (nonspecific) toxicity. On the other hand, if developmental effects are seen at several doses including those at lower doses than for adult toxicity, the degree of concern could increase. The degree of concern is also influenced by the adequacy of the characterization of the dose-response curve at lower dose levels. For example, when the dose-response relationship is well-characterized, i.e., the NOAELs or BMD are defined, there is a lower degree of concern than when the definition of the NOAEL or BMD is poor; in the latter case, the degree of concern may increase.

C. Degree of Concern with Respect to Toxicokinetic and Mechanistic Information-Interpretation of the Human Relevance of Experimental Animal Data

The Agency’s risk assessment guidelines take public health protective positions regarding the interpretation of toxicological information, in that animal findings are assumed to be relevant to humans, unless there is information to the contrary. When available, information on toxicokinetics (processes that determine dose to the target tissue) and mechanism of toxicity (processes that determine the adverse effect) is key to: determining the relevance of animal findings (including whether animals are more or less sensitive compared to humans); identifying whether chemical exposures differentially affect children compared to adults; and guiding the appropriate dose-response extrapolation method.

When toxicokinetic and mechanistic data are available, this information can have a major impact on the degree of concern. For example, toxicokinetic data in animals suggesting that the young are more sensitive compared to adult animals due to a lesser capability to detoxify the parent compound or active metabolite would raise concern. Mechanistic or mode of action information is also important in understanding whether a particular effect may lead to consequences of greater or lesser concern. For example, a transient reduction in anogenital distance in the postnatal animal following perinatal exposure

would lead to concern about other possible effects, e.g., on pubertal development, if the chemical is known to be an antiandrogen. On the other hand, information showing that the chemical affects a species-specific protein or pathway in the laboratory animal would diminish the concern for the observed effect. Although response data showing effects in one species, but not others, might result in a low degree of concern, these data need to be considered in light of what is known about toxicokinetics and mode of action in humans compared to the test species, and the overall quality and robustness of the database. Guidance on evaluating mode of action data can be found in EPA's 1999 draft revised Cancer Guidelines (USEPA 1999e) and OPP's Common Mechanism Guidance Document (USEPA 1999f).

D. Summary

In summary, a weight-of-evidence approach for making judgments about the degree of concern for potential pre- and postnatal toxicity in humans should be conducted when assessing risks to infants and children and in determining whether the default FQPA safety factor is retained or some different value is assigned. As discussed above, this weight-of-evidence approach considers several factors including: available 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 animal data to humans, including toxicokinetics, similarity of the biological response in more than one species, and knowledge of the mechanism of action. Aspects of degree of concern are taken into account in the RfD/uncertainty factor process. For example, all pertinent data are currently considered in the process of calculating acute and chronic RfDs. Furthermore, when data indicate that developmental effects are the most sensitive or critical effects, the developmental effects are well-characterized, and/or appropriate uncertainty factors are applied to the BMDs or NOAELs for these developmental effects to calculate the RfD(s), there would normally be no need for an additional FQPA safety factor to address potential pre- and postnatal toxicity. To the extent that a high concern regarding pre- and postnatal toxicity cannot be addressed through the setting of the RfD, the residual concerns or uncertainties should be addressed through retention of the default FQPA safety factor or use of a special safety factor in the final stage of the risk assessment process.

V. Exposure Considerations Related to the Assessment of Risk to Infants and Children

This section describes the general approaches used in a weight-of-evidence evaluation of the "completeness of data with respect to exposure ... to infants and children" that should be considered when evaluating whether reliable data are available to support a FQPA safety factor different from the default 10X FQPA safety factor and what level of "different" FQPA safety factor would be safe for infants and children.

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. An analysis should be performed for each pesticide using a weight-of-evidence approach to determine the completeness and reliability of the exposure database for that pesticide. 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, the aggregate exposure assessment should use a probabilistic multiroute and multipathway model to develop population exposure distributions. A probabilistic analysis will permit consideration of the full range of model inputs in the exposure assessment.

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 does not underestimate those exposures that are critical for assessing the risks to infants and children. A determination of *low level of confidence* would reflect a conclusion that the assessment was inadequate to judge whether or not exposure was overestimated, underestimated, or accurately estimated. The determination of the level of confidence should 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. The risk assessor should also refer to several Agency guidance documents including the guidelines for estimating exposures (USEPA 1992a), guidance for assessing aggregate exposure (USEPA 1999g and 2001c), and the Exposure Factors Handbook (USEPA 1999h).

1. Food

40 CFR 158.240 sets out the residue data requirements (both Tier 1 and Tier 2, conditionally required and "triggered," respectively) for "conventional chemical" food-use pesticides. These data assist in determining the potential for exposure to pesticide residues resulting from consumption of food. They include:

- Nature of the residue in plants (i.e., the crop that becomes a human food source);
- Nature of the residue in animals (when the animal is a human food source);
- Magnitude of the residue in:
  - crop field trial data,
  - processed food/feed (if the crop is a feed source for an animal which is a human food source),
  - meat, milk, poultry, eggs (if an animal is fed the treated crop and it is a human food source),
  - fish (if the use is aquatic); and
- Reduction of residues (resulting data provide more accurate estimates 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 (e.g., data on "percent crops treated"), provide the basis for a food exposure assessment. Acute and chronic dietary exposures to pesticides in foods are estimated using 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 (USEPA 1998b). OPP began reviewing probabilistic methodologies in 1995; however, the first tolerance action relying on a probabilistic risk assessment did not occur until 1997 (see USEPA 1997a). Probabilistic techniques 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 food and water. Probabilistic exposure assessment models combine these distributional data using numerical methods and algorithms that link pesticide concentrations in foods with food consumption survey data. These models also allow for the description of interindividual variability in exposures.

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). They can then be refined using more realistic values for pesticide residues (for example, using the full range of residues from field trials), corrections for percent of crop treated, and adjustments for the impact of processing (washing, peeling and cooking) to produce better estimates of pesticide residues in food at the time of consumption. Monitoring data from sources such as USDA’s Pesticide Data Program (PDP) or FDA’s Total Diet Study may also be used as sources of pesticide concentration data to produce a more highly refined assessment.

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 inputs and residue data sets to reduce uncertainties associated with current data sets.

Surveys currently accepted by 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 and its 1998 supplemental survey of children. The supplemental survey of children greatly expands the number of infants and children, and thus provides more robust estimates of food consumption for children. These surveys were designed to monitor food use and food consumption patterns in the U.S. population. The data were collected as a multistage, stratified, probability sample that was representative of the U.S. population. These surveys consist of food consumption data obtained over two or three days based on questionnaires completed by the consumer. The most recent survey (CSFII 1994-1996/1998) 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 U.S. population.

OPP considers the CSFII data adequate to model the daily variability in the U.S. diet. Chronic population exposures are generally estimated using the average consumption for a given population or subset of a given population. Demographic information collected as part of the surveys allows classification of food consumption information by categories such as age groups and provides meaningful distributions for consumption patterns. Care must be taken when determining what foods drive an unacceptable exposure assessment to ensure that potential risk to children is not overlooked.

For the assessment of acute dietary risk for infants and children, the NSCF and CSFII surveys provide adequate, high quality data to model distributional patterns. Using these data, the Agency currently addresses total population and population subgroup risk for a variety of age groups. Age groups for children are currently <1, 1 to 2, 3 to 5, 6 to 12, and 1 to 19 years. These age groups are defined such that they reflect an adequate number of individuals in each age group and are based on real differences in age-related eating patterns.

2. Drinking Water

For each use of a pesticide (with existing or pending U.S. registrations), an assessment must be conducted of the potential for that compound to reach drinking water sources or supplies. Data requirements of 40 CFR 158 include:

Magnitude of the residues in potable water (aquatic use)

Degradation studies-lab

Photodegradation in water, soil, and air

Metabolism studies in soil and water (depending upon use site)

Mobility studies on leaching and adsorption/desorption, and volatility

Dissipation studies in the field on soil (terrestrial use) and sediment (aquatic use)

Prospective groundwater monitoring study

Data from these studies and estimated concentrations from monitoring and modeling data in raw and finished drinking water from a variety of sources along with data on water consumption by humans are combined in a variety of ways to provide a perspective on the likelihood that the pesticide will occur in drinking water and an estimate of the level of concentration. 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. The early tiers employ a deterministic approach to the analysis and the more refined tiers employ a probabilistic assessment using distributions of potential concentrations of pesticides in drinking water sources and distributions of water consumption in the U.S. population.

OPP scientists use pesticide-specific data as inputs to

models (FIRST and PCA used with PRZM/EXAMS for surface water and SCI-GROW for groundwater). These models allow development of estimates of pesticide concentrations in surface water and groundwater. FIRST and PCA used with the PRZM/EXAMS models are mechanistic models built on 36 years of weather data and data on the key characteristic of pesticides that determine how they are likely to move in the environment. SCI-GROW was developed at OPP and is an empirical (linear-regression) model based on the results of small-scale prospective groundwater studies. OPP generally views the estimates coming out of these models as "high-end" or "upper-bound" estimates of potential pesticide concentrations in drinking water. During this stage of the process, OPP reviews in-house water monitoring data to ensure 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.

Model estimates of potential pesticide levels in drinking water are compared to human health-based "drinking water levels of comparison" or "DWLOCs." DWLOCs represent a theoretical maximum concentration for a pesticide in drinking water (after having first considered all food-related and residential exposures) that results in a risk estimate of no concern to OPP. Based on this comparison, the pesticide is either cleared as a potential risk from a drinking water perspective, or OPP attempts to refine the estimates of pesticide concentrations in order to make them more realistic.

If the determination is made to refine these estimates, additional water monitoring data are gathered and additional analyses are conducted at higher tiers. 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 database, the data from the USGS Mid-Continent Group, OPP’s Pesticides in Groundwater Data Base, and the National Pesticide Survey, and in-house studies conducted by registrants and submitted to the Agency 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 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 percent 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 that 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 for each exposure scenario as appropriate. The results of the analysis, including characterization of monitoring and modeling data used, are integrated with food and residential exposure analyses to complete the aggregate exposure assessment (USEPA 2000d).

3. Residential and Other Non-Occupational Exposure

When compared with the number of studies required in other areas of risk assessment such as toxicology or food exposure, the number of studies required in 40 CFR 158 that assist in the understanding of "residential" and other nondietary, nonoccupational 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:

Foliar dissipation

Soil dissipation

Dermal exposure (unless surrogate data are available)

Inhalation exposure (unless surrogate data are available)

Even though chemical-specific data are sparse, adequate residential exposure assessments that do not underestimate exposure 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 that 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" (USEPA 1997b). The objective of these SOPs is to provide high-end screening level methods (models and exposure factors) for developing residential assessments for both handler and postapplication exposures when chemical-specific data for one or more model input parameters is not available. 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 residential and other nonoccupational settings 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 SAP in September, 1997 and received public notice and comment review. They have been expanded and revised on the basis of these comments. Important aspects of the revisions are the 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.

B. How the Approaches for Assessing Single Exposure Route and Pathways Compensate for Database Deficiencies

For the most part, OPP is developing assessments that reflect only those exposures directly resulting as a consequence of an approved or requested use of a pesticide. These exposures occur by three broad pathways: food, drinking water, and residential. In fact, the term "residential" may be somewhat misleading because this term encompasses more exposure scenarios than that term would indicate. It also includes exposures to the general public that would arise from the use of pesticides in schools and day care centers, offices, golf courses, 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 that are the direct consequence of an approved pesticide use (e.g., nonpesticidal uses of a commodity chemical in a consumer product).

1. 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, underestimation or overestimation of dietary exposure may occur. 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.

2. 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 high-end or upper-bound estimates of potential pesticide concentrations in drinking water. As such, they generally yield assessments having a **high level of confidence** because they are sufficiently conservative to adequately protect infants and children via this pathway.

3. Residential and Other Nonoccupational Exposure

The nonoccupational, 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. For exposure scenarios in which data are incomplete, if some of the known exposure scenarios have not or cannot be addressed currently, or if the default assumptions used to estimate exposure 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 may be taken into account by incorporating a special factor during the FQPA safety factor decision process.

It should be understood, however, that because not all possible 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 (USEPA 1997b) mirror the strategy for creating reasonable high-end scenarios as indicated in the EPA's *Dermal Exposure Assessment: Principles and Applications* (USEPA 1992b). 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 (USEPA 1999k). 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

Traditionally, pre-FQPA, OPP's exposure assessments were focused on a single chemical and single route of exposure. Exposures and resultant risks were expressed individually by pathway and chemical, not as combined exposures or risks. FQPA mandates consideration of aggregate exposures to pesticides from food, drinking water, and all other nonoccupational 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 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 that these exposure assessments are protective of infants and children.

OPP's document on principles for conducting aggregate risk assessments (USEPA 2001c) provides guidance for combining risks by route. In February 1999, a draft of this document (USEPA 1999g) was discussed at an SAP meeting. Among the topics, OPP discussed the desirability and need for the development and use of probabilistic techniques, instead of, or in addition to, the existing deterministic methods. A Monte Carlo simulation system was proposed to be used in the probabilistic pesticide exposure/dose model, which would simulate the variability in the concentrations or exposure factors. Acute, short-term, intermediate-term, and chronic average exposures/doses to selected pesticides eventually can be predicted based on various scenarios of pesticide use. The model's outputs will provide information on estimates of interindividual variability in the population exposure or dose.

D. Evaluation of Potential Residual Uncertainties in the Exposure Assessment

OPP's exposure assessments use a combination of approaches to assure that potential exposure is generally not underestimated. OPP recognizes that, in some limited situations, its exposure estimates may not have addressed all significant exposure routes or there may be uncertainty about whether OPP's approach to estimating exposure for a particular use pattern, pathway, or aggregate exposure is sufficiently health protective. Therefore, in the final stage of the risk assessment process, the risk assessor should evaluate for each pesticide the potential that its use-specific, pathway-specific, and aggregate exposure assessments may underestimate potential exposure. If there is uncertainty concerning whether exposure to infants and children has been adequately estimated, the default 10X additional safety factor should be retained unless there is reliable data showing that selection of a different FQPA factor (referred to by this document as a "special FQPA safety factor") will be safe for infants and children. As with other factors, this evaluation should take all relevant information on exposure into account and make judgments on the basis of the weight-of-evidence. Moreover, because this evaluation will occur during the integrative analysis discussed below in Section VI, OPP also intends to consider the degree of conservatism in other aspects of the risk assessment. The rest of this Section discusses the recommended approach for assessing the degree of conservatism in the exposure assessments.

First, decision-makers should consider on a case-by-case basis whether significant exposure could be occurring for a major identifiable subgroup of consumers through an exposure scenario that has not been evaluated. Depending on the characteristics of the pesticide and its use sites, a number of different exposure scenarios might be sufficiently plausible to merit attention. For example, in appropriate circumstances, decision-makers may need to consider whether levels of the pesticide in the ambient environment could result in residues in fish or shellfish or other foods that may make significant contributions to overall dietary exposure. In addition, depending on the use pattern of the pesticide, decision-makers may also need to evaluate the potential contributions to dietary exposure from outdoor residential use of pesticides that could run off into surface water or leach into groundwater used as sources of drinking water. Risk assessors should also consider whether exposure to degradation products to which people may be exposed has been adequately evaluated. Further, decision-makers should look at whether the chemical has any other uses either for pesticidal or nonpesticidal purposes that could result in significant nonoccupational exposure. Although models and data to evaluate some of these possible exposure scenarios may be limited, decision-makers should use a range of other information for

example, usage data, toxicokinetics information, physical and chemical characteristics, environmental fate data to predict qualitatively whether such scenarios could contribute significantly to exposure.

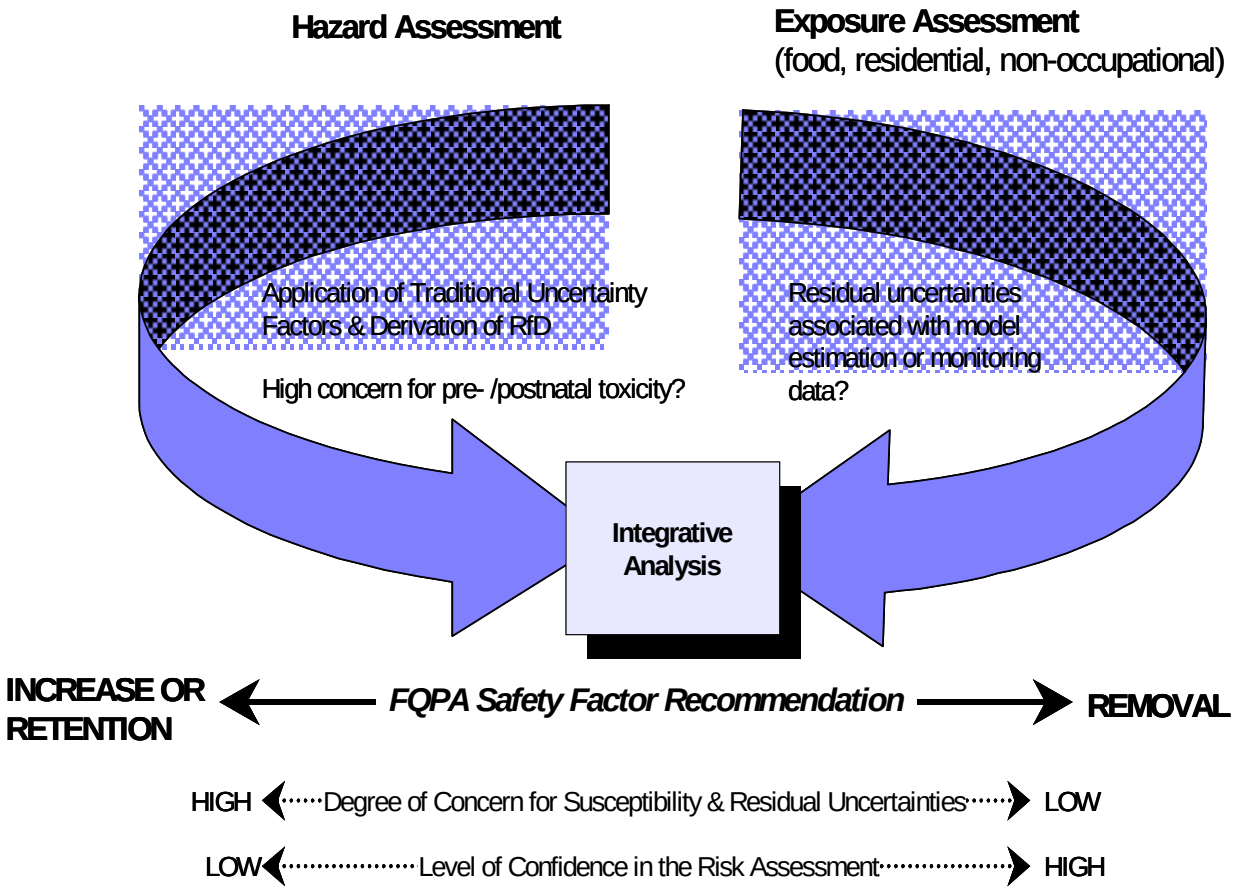
Second, the risk assessor should consider whether the manner in which exposures for a particular pathway or the aggregate exposure estimate may tend to overstate or understate potential exposure. The risk assessor should examine whether the manner in which exposures from multiple uses are combined in a pathway or aggregate assessment may tend to overstate risk. Thus, the overall judgment about the conservativeness of the exposure assessment and/or the potential need for and adequacy of a special FQPA safety factor to protect infants and children should take all available information into account. The risk assessor should document this additional evaluation during the risk characterization step.

VI. Risk Characterization

A. Integration of Toxicity and Exposure Considerations

The decision to retain the default 10X FQPA safety factor or to assign a different safety factor is informed by the conclusions presented in the risk characterization, i.e., the final step in the risk assessment process. As shown in Figure 5, the risk characterization is an integration step wherein the weight-of-evidence analyses for the completeness of the toxicity database, the degree of concern for pre- and postnatal toxicity, and results of the exposure assessments are combined by decision-makers in evaluating whether the presumptive 10X safety factor should be retained or reliable data justify a different factor that could range from a level of 1X to 10X, and possibility greater than 10X.

Figure 5. Consideration of the FQPA Safety Factor in Risk Characterization



This risk characterization step provides an evaluation of the overall quality of the assessment including confidence in the conclusions and residual uncertainties, as well as an evaluation of whether the standard approach for deriving RfDs (or RfCs) by applying traditional uncertainty factors provides assurance that infants and children will be adequately protected. The risk characterization describes risk in terms of the nature and extent of harm, and communicates the results of the risk assessment to the risk manager. Risk assessors and risk managers should engage in extensive dialog to ensure that all aspects of the risk assessment are understood by risk managers, that there is adequate scientific basis for the decision, that the information is clearly understood and articulated, and that sound scientific judgment prevails. Guidance on conducting risk characterizations can be found in the Agency's Handbook (USEPA 2000c).

B. Principles for FQPA Safety Factor Decisions

The starting point for analysis of the FQPA safety factor begins with the statutory provision. As stated previously, the 10X safety factor under FQPA is intended to take into account three areas: the completeness and reliability of the toxicology database (Section III), the potential for pre- and postnatal effects (Section IV), and the completeness and reliability of the exposure database (Section V). At the integration stage of its analysis, OPP needs to determine whether residual concerns remain about the way in which the risk assessment process handled completeness of the toxicology and exposure databases and potential for pre- and postnatal toxicity of the FQPA safety factor mandate. It is important that the risk assessor is mindful of areas where the FQPA factor incorporates traditional uncertainty factors (i.e., toxicity data deficiencies) versus those areas where the FQPA factor involves special consideration related to the regulation of pesticide residues in food (i.e., residual concern for pre- and postnatal toxicity, and exposure uncertainties).

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 presumption in favor of the additional 10X default FQPA safety factor would be obviated and the risk assessor should recommend that a different FQPA safety factor be applied, generally just 1X, so as not to increase the overall safety factor beyond the standard inter- and intraspecies safety factors. 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 the risk assessor could conclude that the departure from an additional 10X safety factor is appropriate, and a different safety factor of 1X

would be sufficient to protect infants and children. Conversely, if the risk assessor finds evidence of pre- or postnatal toxicity or problems with the completeness of the toxicity or exposure databases and these uncertainties have not been adequately dealt with in the toxicity and/or exposure assessments (through use of traditional uncertainty factors or conservative exposure assumptions), then the default additional 10X safety factor should be retained. Alternatively, a different FQPA safety factor greater than 1X may be used to address evidence of pre- or postnatal toxicity or problems with the completeness of the toxicity or exposure databases when reliable data are available that permits these concerns to be adequately addressed either in the toxicity or exposure assessments (through the use of traditional uncertainty factors or conservative exposure assumptions) or at the risk characterization stage (through the use of a special FQPA factor).

Because OPP often establishes different RfDs or MOEs for different exposure scenarios, there may be more than one FQPA safety factor decision made for each aggregate risk assessment conducted for a single active ingredient and they may be different from one another. Separate decisions may be necessary for: (1) different population subgroups being evaluated; and (2) different durations of exposure (e.g., acute, short-, intermediate-, long-term). While separate preliminary decisions may be made for each different exposure scenario when assembling an aggregate assessment, final 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 are:

> One each for one or more age groups of infants and children for up to three durations of exposure (i.e., acute, intermediate-term, chronic);
>
> 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; and
>
> One each for sexually mature males (based on concern for heritable germ cell effects) 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.

Once the decision is made to use either the default 10X FQPA safety factor or a different FQPA safety factor to address the potential for pre- and postnatal toxicity, and the completeness

of the toxicity and exposure databases, such a factor, to the extent it is comprised of components above and beyond those considered in the traditional uncertainty factors, should be used to address the adequacy and acceptability of the calculated margin of exposure (MOE) or the RfD. If a special FQPA factor is applied, the RfD is altered. OPP defines this FQPA-corrected RfD as the Population Adjusted Dose (PAD):

$$PAD = \frac{RfD}{\text{Special FQPA Safety Factor}}$$

If effect(s) in the young raise a high concern for susceptibility due to residual uncertainties for an endpoint different then that used to derive the RfD, than the BMD or NOAEL for that effect should be divided by the appropriate uncertainty factors and the FQPA safety factor and compared with the RfD. The lower of the two values should be used as the PAD. When exposure deficiencies are the primary factor, the RfD is adjusted by the special FQPA safety factor for the population and exposure duration of interest, effectively resulting in a PAD that is at a lower dose than the RfD. If there are residual concerns for both exposure and toxicity, then the RfD should be considered and adjusted appropriately as discussed above, again resulting in a PAD lower than that for the RfD.

APPENDIX: Legal Framework

I. 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."

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." This document will refer to this section of the statute as the FQPA safety factor provision.

In addition to the FQPA safety factor provision, Section 408(b)(2)(D) of the amended statute also directs EPA "[i]n establishing, leaving in effect, or revoking a tolerance or exemption for a pesticide chemical residue" to "consider, among other relevant factors:"

> Validity, completeness and reliability of available data (see Section 408(b)(2)(D)(i));
>
> Nature of any toxic effect caused by the pesticide (see Section 408(b)(2)(D)(ii));
>
> Relationship of the results of toxicity data to human risk (see Section 408(b)(2)(D)(iii));

Dietary consumption patterns of consumers and major identifiable subgroups of consumers (see Section 408(b)(2)(D)(iv));

Cumulative effects of any pesticides and other substance that have a common mechanism of toxicity (see section 408(b)(2)(D)(v));

Aggregate exposure levels of consumers, and major identifiable subgroups of consumers, from non-occupational sources (see section 408(b)(2)(D)(vi));

Variability of the sensitivities of major identifiable subgroups of consumers (see section 408(b)(2)(D)(vii));

Whether the pesticide may have an effect in humans that is similar to effects caused by naturally occurring estrogen or other endocrine effects (see section 408(b)(2)(D)(viii)); and

Safety factors appropriate for the use with experimental data in animals (see section 408(b)(2)(D)(ix)).

II. Key Interpretational Issues

A. 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 determining the dose level at which no adverse effects were seen in animal studies and adjusting that numerical value by applying "safety factors" designed to account for, among other things, potential differences between animals and humans and potential differences among humans (commonly referred to as the inter- and intraspecies factors). Because the factors cannot guarantee absolute safety and the factors are used to address uncertainties in the knowledge base, more recently, EPA has begun using the term "uncertainty factors" instead of "safety factors." Given that EPA has used both terms to address the same concept and Congress clearly intended the FQPA safety 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 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," since the **statute** uses the term "**safety factor**," OPP will continue to use the term "safety factor" when referring to the factor applied for the protection of infants and children.

B. 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 serves 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 tenfold safety or uncertainty factors when relying on animal testing to assess the potential for human hazard posed by exposure to chemicals. The two tenfold factors used most often are designed to address both the extrapolation of the results of animal studies to humans (i.e., the interspecies uncertainty factor) and variability and sensitivity within humans (i.e., intraspecies uncertainty factor) 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 intraspecies factors where the circumstances warrant such factors. These uncertainty factors have been used principally to address gaps in the toxicology database or inadequacies in the key existing toxicology studies. For food use pesticides, it has only occasionally been necessary to apply additional uncertainty factors to account for gaps or inadequacies of this nature. Considering these past risk assessment and regulatory practices and the considerable overlap between the FQPA safety factor and existing practice on the use of additional factors (see B.3. below), OPP believes Congress intended that the FQPA safety factor be in addition to only the standard, baseline inter- and intra-species uncertainty factors.

C. 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 safety factor is added, but OPP's pre-FQPA use

of the other uncertainty factors helps to provide content to the FQPA safety factor itself. It is OPP's view that the FQPA codifies OPP's pre-FQPA use of traditional uncertainty factors in addition to the standard inter- and intra-species factors. For example, as noted, traditional uncertainty factors have been used by OPP specifically (and EPA more broadly) 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 pre-FQPA uncertainty factors which address deficiencies in the toxicology database regarding effects of concern for all populations, including infants and children, have become, after passage of the FQPA, FQPA safety factors. 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," Congress intended that OPP apply its traditional deficiency 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.[7] 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 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 or uncertainty factor approach with exposure assessments. That is, OPP did not modify exposure assessments by

[7]Contrary to statements in the NAS 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.

some factor to address limitations 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.

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

The statute established that OPP shall 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 provides that OPP may apply a different safety factor where reliable data show that such a factor will be safe for infants and children. OPP interprets these statutory directives as essentially establishing a presumption in favor of applying an additional 10X safety factor to pesticide risk assessments. Only when there is reliable evidence showing that a different safety factor is protective of infants and children would it be appropriate not to retain the presumptive or default 10X factor. As explained in the policy document, OPP favors an approach relying to the greatest extent possible on reliable data to make individualized assessments for pesticides of the appropriate, if any, additional safety factor needed to protect infants and children.

In evaluating the size of any factor different from the 10X default safety factor, 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. Rather, OPP thinks that its focus should be on what factor is needed to protect infants and children. That analysis should concentrate on what the existing data show with regard to the pesticide in question. When data are missing or otherwise incomplete, the analysis will be concerned with how the results from the missing data could affect the risk assessment. This analysis may result in a finding that a factor either greater or less than 10X should be added to the traditional inter- and intraspecies factors or that no factor in addition to these traditional factors is needed. It may also result in the conclusion that an additional factor of 10X is needed 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. OPP has become concerned that use of the language "retain, reduce or remove" 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. OPP continues to adhere to the core principle that the FQPA establishes an additional 10X safety factor as a default. In this document the phrase "consider an FQPA safety factor" should be interpreted to mean to retain the presumptive 10X FQPA safety factor or to establish a different safety factor that is less than, equal to, or greater than the default value.

E. 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., *Section 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 such that OPP 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 a 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. However, for many pesticides, 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 tenfold default value for the protection of infants and children, this policy directs the risk assessor to focus on whether the assumption or model is based on a combination of data and 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 completely 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.

F. What Pesticides Are 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. For the purpose of FQPA and the scope of the FQPA safety factor guidance, the term "pesticide" covers both active and other (i.e., inert) ingredients. In the U.S., at the present time, there are nearly 1000 pesticides registered as active ingredients and about 2500 pesticides registered as "other" ingredients. Food use pesticides, both actives (over 450 in number) and others, belong to many chemical classes. The chemical characteristics and anticipated toxicity potential of the pesticide (along with the proposed use pattern) dictate the kinds of toxicology data that would be needed to characterize its hazard profile. For those categories of food-use pesticides for which only a minimum toxicology database is deemed necessary, a "reasonable certainty of no harm" and safety factor finding would be accomplished only in the *qualitative* sense, particularly those for which an exemption from a tolerance would be granted. A similar qualitative approach to the FQPA safety factor would generally be followed. The Agency believes that there are many examples of substances that might be subjected only to a

qualitative finding, such as the active components in plant incorporated pesticides, microbial and some other biopesticides, as well as many inert ingredients. For many others, including most of the pesticides thought of as "conventional" chemicals, the required toxicity database is larger and more diverse in endpoints evaluated and, as such, would lend themselves to *quantitative* FQPA safety factor decisions. That is, numerical values would be derived, then modified upward, downward or left unchanged during the FQPA safety factor decision process, depending upon the nature and fullness of the available information. Examples of classes more traditionally thought of as "conventional" pesticides are the organophosphorous and pyrethroid insecticides; the triazine, chlorphenoxy, and chloracetanilide herbicides; and the conazole fungicides.

The statute requires that no tolerance or tolerance exemption may be granted for an FFDCA "pesticide chemical" without adhering to the children's safety provision in section 408(b)(2)(C) including the additional safety factor requirement in that provision. The FFDCA defines a "pesticide chemical" as "any substance that is a "pesticide" within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act," excepting certain antimicrobial pesticides (see FFDCA section 402 (q)(1)(B); 21 U.S.C. 321(q)(1)(B) as amended by the Antimicrobial Regulation Technical Corrections Act of 1998, Pub. L. 105-324, 112 Stat. 3035 (1998)). Thus, if a pesticide has a use that qualifies as a "pesticide chemical" and that use requires a tolerance or exemption from tolerance (i.e., the use results in residues in or on food), that pesticide would have to be evaluated under section 408(b)(2)(C). Further, section 2(bb) of FIFRA specifies that a pesticide cannot meet the regulatory standard under FIFRA if "a human dietary risk from residues that result from a use of [the] pesticide in or on food [is] inconsistent with the standard under section 408 of the Drug, and Cosmetic Act." EPA interprets this language as imposing a similar test to that under section 408 pertaining to whether a tolerance is needed that is, a determination of whether the use of the pesticide results in a dietary risk due to residues in or on food. The scope of FIFRA section 2(bb), however, is slightly broader than section 408 because section 2(bb) applies to FIFRA "pesticides" not only FFDCA "pesticide chemicals." Thus, any pesticide that has a use captured by FIFRA section 2(bb) would need to be analyzed under the children's safety provision even if the use is excluded from section 408 by the definition of "pesticide chemical."

It has been argued that, if the only action before the Agency is an application for the registration of a use of a pesticide that does not result in residues in or on food, then a children's safety factor analysis is not required even if the pesticide has other uses which result in residues in food. Whether or not a children's safety factor analysis is strictly required to make the FIFRA registration decision for that non-food use, OPP does not believe it would be wise to register such a use without considering the children's safety factor provision as well as the other provisions in section 408 concerning risk assessment. Proceeding without consideration of section 408 and the effect that the new use will have on the aggregate risk as it applies to the existing uses covered by section 408 might lead to a situation where OPP would grant the non-food use only to have to immediately cancel that use or some other use because of aggregate risk concerns under the FFDCA. If a pesticide has no uses that result in dietary risk as a result of residues in or on food, then there would be no legal requirement to do a children's safety factor analysis under FFDCA section 408(b)(2)(C). OPP, nonetheless, may wish to consider the mode of analysis followed under the children's safety provision to ensure that any action under FIFRA fully considers the potential risks to children.

G. What Population Subgroups Are 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 adverse effects 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 is generally considered to span the age range from 18-21 years of age) or females of child-bearing age (characterized as "females aged 13 - 50" in OPP risk assessment policies and procedures) 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 pesticide exposure to the male sperm cells 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.

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